Chlorinated quinolines, isoquinolines and their benzo derivatives

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UNIVERSITY OF DURHAM

A THESIS

entitled

CHLORINATED QUINOLINES, ISOQUINOLINES AND THEIR BENZO DERIVATIVES

submitted by

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A candidate for the degree of Doctor of Philosophy

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To my Mother and Father

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Thanks are due to many technical and laboratory staff for their assistance, and particularly to Mrs. E. McGauley for the helpful way in which she typed this thesis.

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MEMORANDUM

The work described in this thesis was carried out at the University of Durham between October 1971 and August 1974. This work has not been submitted for any other degree and is the original work of the author except where acknowledged by reference.

SUMMARY

Three fully chlorinated heterocyclic compounds, nonachloroacridine, nonachlorophenanthridine and nonachloro-7,8-benzoquinoline, have been synthesised by direct chlorination of the appropriate ring systems. It has been shown that halogen exchange by alkali metal fluorides, in a solvent or in the solid phase, fails with these compounds containing three fused rings.

Nonachloroacridine and nonachlorophenanthridine underwent nucleophilic monosubstitution in the 9- and 6-positions respectively, but with larger nucleophiles that were better electron donors, non-specific reductive dechlorination occurred instead. Acid induced hydrolysis has been shown to occur in the 9- and 6-positions, and has shown that nonachloroacridine is more basic than nonachlorophenanthridine.

Nucleophilic substitution of heptachloroquinoline and heptachloroisoquinoline has also been investigated. It has been shown that heptachloroquinoline undergoes substitution in the 2-position, and much less readily in the 4-position, probably because of steric effects. Heptachloroisoquinoline would only undergo monosubstitution, in the 1-position. The possibility of using carbon-13 n.m.r. to assign the position of the substituent was investigated but, despite some success, difficulties of assignment limit the value of the technique at present. In attempts to make model compounds for carbon-13 n.m.r. work, it was found that octachloronaphthalene was quite resistant to nucleophilic attack, but underwent reductive dechlorination quite extensively.

Perfluoro-5,6,7,8-tetrahydroquinoline has been prepared from 5,6,7,8-tetrachloroheptafluoroquinoline by halogen exchange in a solvent, and 5,6,7,8-tetrachloroheptafluoroisoquinoline has been prepared and similarly converted to perfluoro-5,6,7,8-tetrahydroisoquinoline. These results confirmed

mechanisms proposed earlier for the formation of the partially saturated fluorinated compounds during autoclave fluorinations of heptachloroquinoline and heptachloroisoquinoline. Polyfluoroalkylation was effected on perfluoro-5,6,7,8-tetrahydroquinoline in the 2- and 4-positions. A range of nucleophiles has been shown to substitute perfluoro-5,6,7,8-tetrahydroisoquinoline in the 3- and then in the 1-positions.

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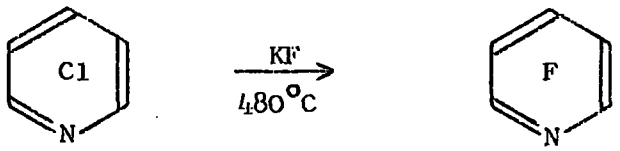
INTRODUCTION

CHAPTER I

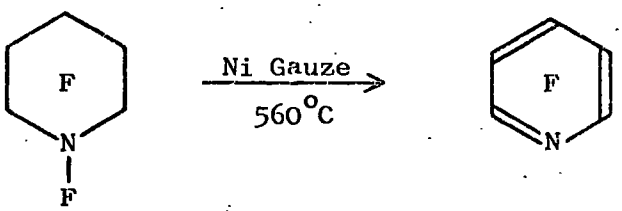
The Synthesis and Properties of Perchlorinated Aromatic Heterocyclic Compounds Containing Nitrogen

1. General Introduction

Since about 1960, many perchloroheterocyclic compounds containing nitrogen have been prepared, frequently by workers interested in perfluoroheterocyclic compounds. This has been because the most convenient way of preparing the perfluoroheterocyclic compounds is by halogen exchange reactions on the perchloroheterocyclic compounds. For example, pentafluoropyridine has been prepared from pentachloropyridine by heating the latter with anhydrous potassium fluoride in an autoclave.[1]



It had been possible to obtain pentafluoropyridine by electrochemical fluorination of pyridine or piperidine, which produces undecafluoropiperidine[2,3] followed by defluorination of the latter in a nickel tube,[4] but this was not a convenient synthetic route to pentafluoropyridine.



The halogen exchange reaction has been found to be much more generally applicable, so many perchloroheterocyclic compounds have been prepared, but their properties have been little investigated compared with all the work reported on the properties of the fluorinated compounds, for two main reasons. First, the low volatility and low solubility of the chlorine compounds make

their handling and separation difficult. Secondly, apart from mass spectrometry, there is no very convenient spectroscopic tool for identifying their structures. This contrasts with the fluorinated compounds which are quite soluble in a wide range of organic solvents, volatile enough to be used in vapour phase chromatography, and suitable for investigation by ^{19}F n.m.r. spectroscopy.

The aim of this work was to investigate the properties of some perchlorinated heteroaromatic compounds where nitrogen is the hetero atom and to synthesise some new perchlorinated systems.

2. Preparation of Perchloroheteroaromatic Compounds Containing Nitrogen

There are two main approaches to the synthesis of these compounds. The first involves direct chlorination of the required ring system, while the second involves cyclisation of a material which is already partly or fully chlorinated, to give a new ring system.

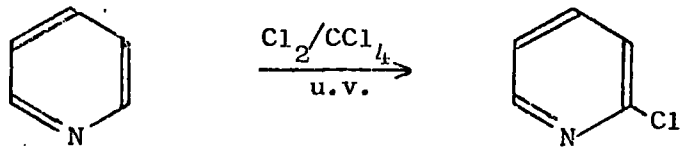
2.1 Methods Involving Direct Chlorination of the Heterocyclic System

The chlorination of heterocyclic compounds in general has been reviewed[5], but this review chiefly deals with reactions in which chlorine is the chlorinating reagent and no catalyst is used. Any classification of these reactions is rather arbitrary and the following classification has been made for convenience only.

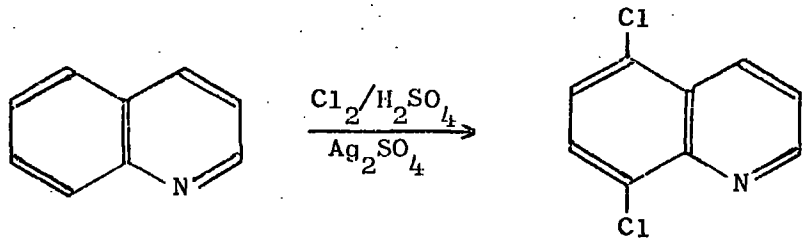
A. Elemental Chlorination in the Liquid or Vapour Phase

Generally, the chlorination of heterocyclic nitrogen compounds in the liquid phase (either as a solution or when the substrate is a liquid) does not lead to a very high degree of chlorination, but rather to a high degree of specificity in the orientation of substitution.

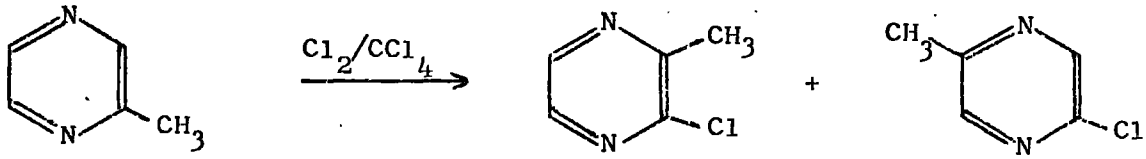
When pyridine in carbon tetrachloride solution is treated with chlorine under ultra-violet irradiation, only 2-chloropyridine is formed.[6]



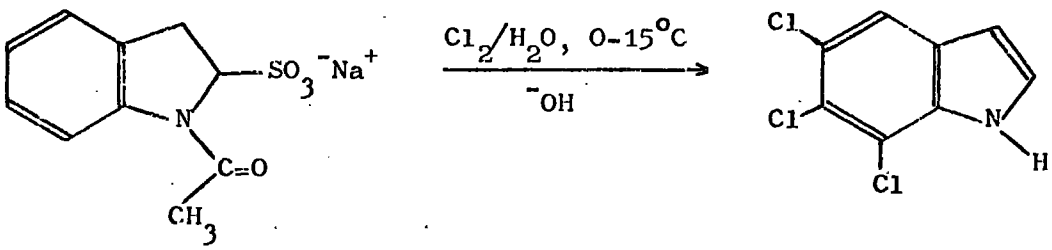
Quinoline is converted exclusively to 5,8-dichloroquinoline by treatment with chlorine, in sulphuric acid solution and in the presence of silver sulphate.[7]



The chlorination of 2-methylpyrazine in carbon tetrachloride, however, is less specific, giving 2-chloro-3-methylpyrazine as well as 2-chloro-5-methylpyrazine.[8]

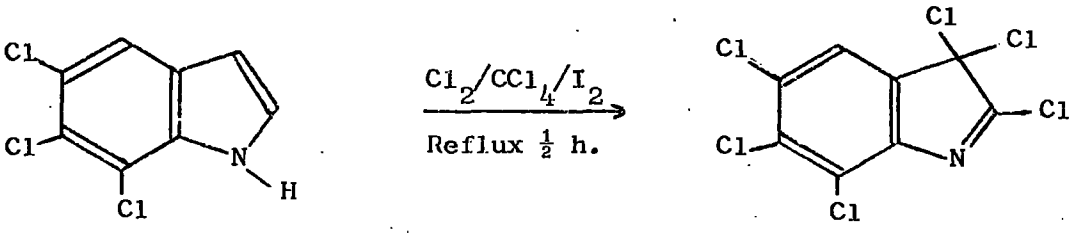


There are some instances, however, where elemental chlorination in solution can lead to a higher degree of substitution. For example, when the sodium salt of N-acetylindoline-2-sulphonic acid is chlorinated in water and the product is base hydrolysed, 5,6,7-trichloroindole is produced.[9]

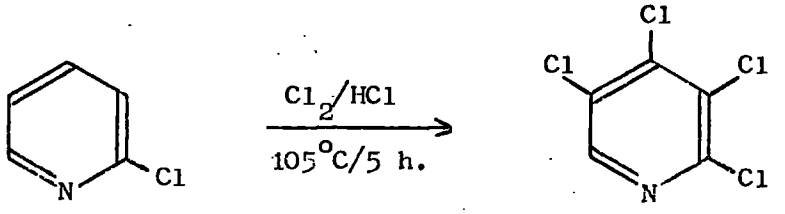


This trichloroindole may be chlorinated further in refluxing carbon tetrachloride, with a trace of iodine as catalyst, to give 2,3,3,5,6,7-

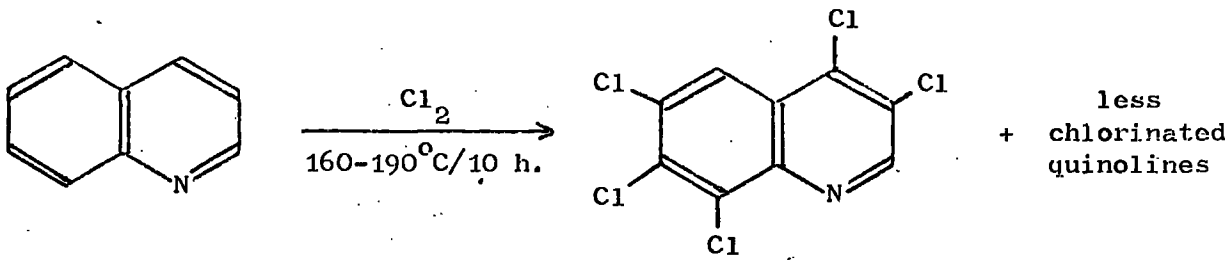
hexachloroindolenine.[10]



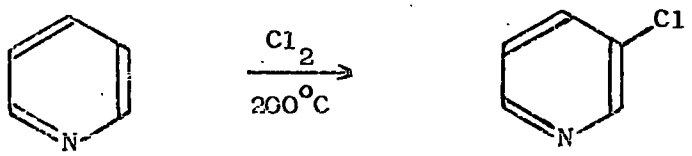
It has also been possible to achieve a higher degree of chlorination in the liquid phase by using more drastic conditions. 2-Chloropyridine is converted to 2,3,4,5-tetrachloropyridine by passing chlorine through a mixture of the hot liquid substrate and hydrochloric acid.[11]

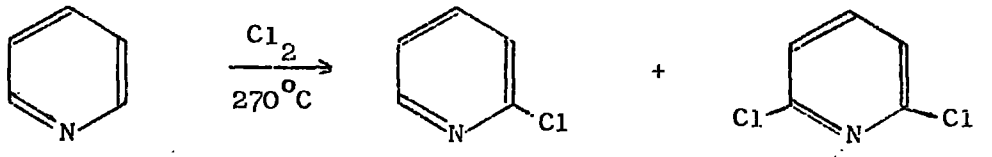


Passing chlorine through heated quinoline gives a mixture of products, including the highly chlorinated 3,4,6,7,8-pentachloroquinoline.[12]

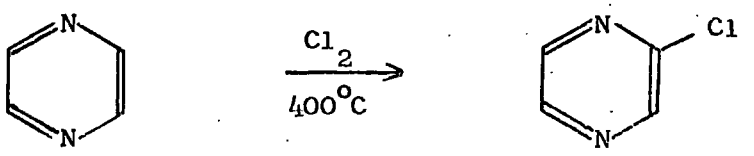


Early work on vapour phase chlorinations did not lead to a very high degree of substitution and the position of substitution was found to be quite variable. At 200°C, pyridine is converted to 3-chloropyridine, whereas at 270°C, it gives a mixture of 2-chloropyridine and 2,6-dichloropyridine.[13]

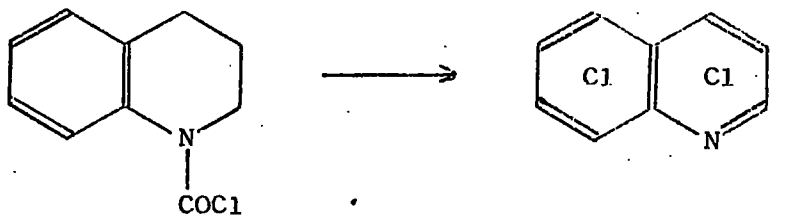




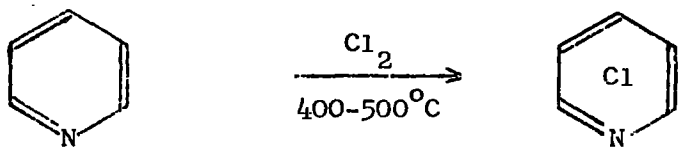
Pyrazine has also been chlorinated in the vapour phase to give the monochloro compound.[14]



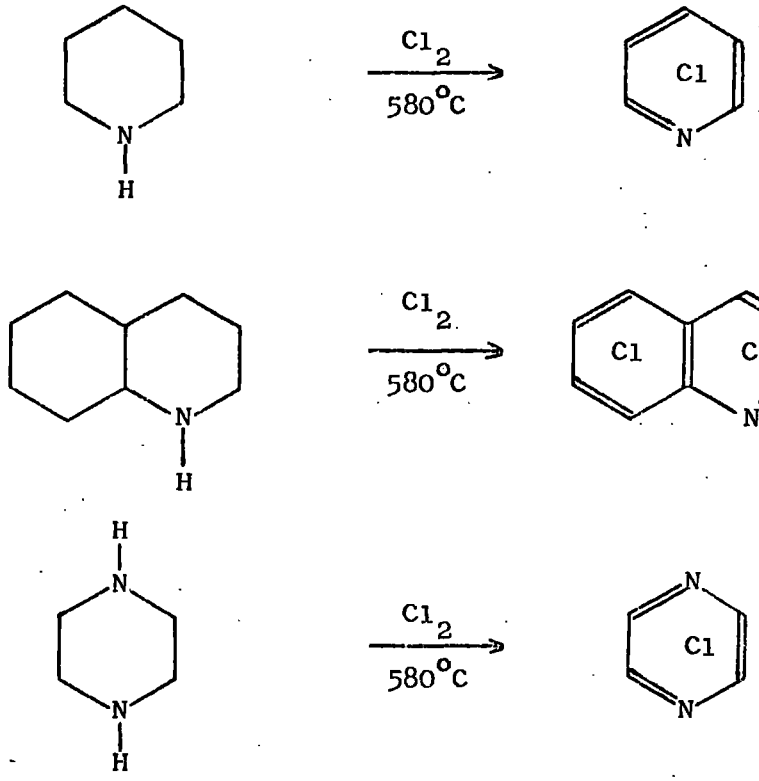
It has been found that the vapour phase chlorination of carbonyl chlorides is a useful synthetic route to some chlorinated heterocyclic compounds.[15] For example, 1,2,3,4-tetrahydroquinoline-N-carbonyl chloride is converted to heptachloroquinoline by pre-chlorination at 50-150°C, followed by chlorination at 150-500°C in the presence of activated carbon.



Recently, higher temperatures and the presence of solids, have allowed full chlorinations of compounds without functional groups to be achieved. Thus pyridine is converted to pentachloropyridine by chlorine gas, diluted with nitrogen or carbon tetrachloride, and in the presence of a siliceous earth.[16]

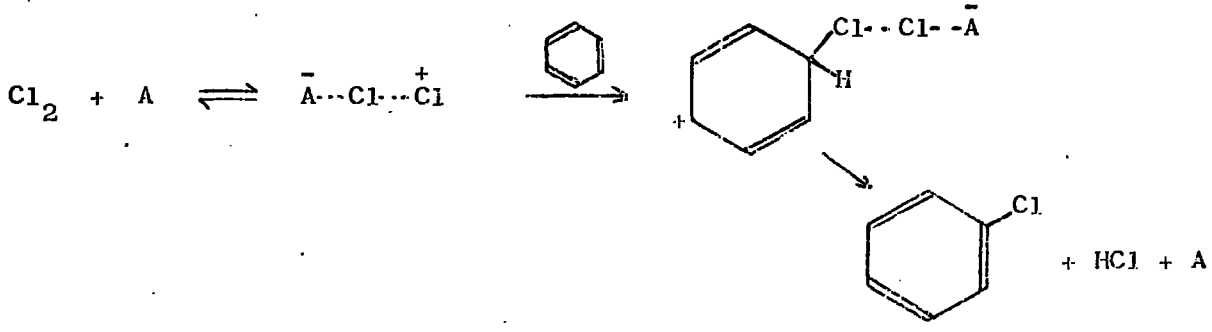


In a rather interesting reaction, pentachloropyridine, heptachloroquinoline and tetrachloropyrazine have been prepared from their saturated hydrocarbon analogues by passing the latter, with chlorine and carbon tetrachloride diluent, down a heated tube.[17]



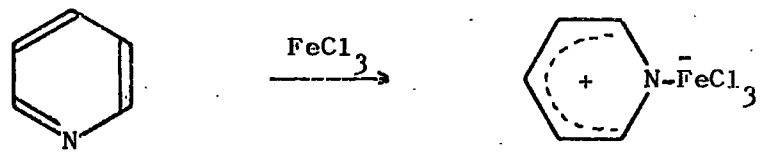
B. Elemental Chlorination with Lewis Acid Catalysts

Chlorination of aromatic systems by Lewis Acid catalysis is a well known reaction, and is believed to proceed by an electrophilic process, in which the catalyst complexes with a chlorine molecule to give a positive chlorine species. The positive chlorine then attacks the aromatic system to give an intermediate which can eliminate a proton to give the product. Thus for a Lewis acceptor A, the chlorination of benzene is believed to occur as follows.

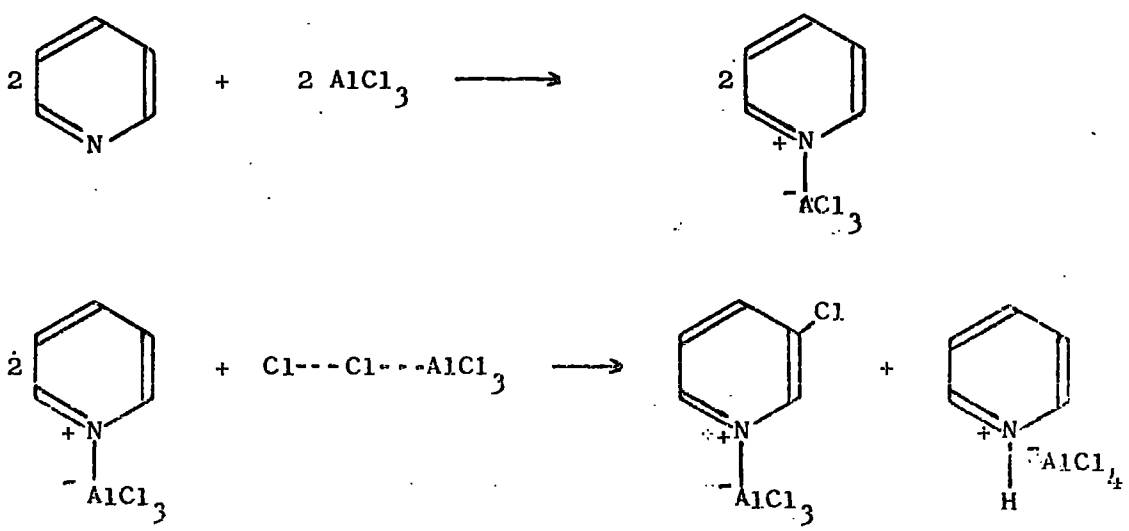


The strength of the complex between the catalyst and chlorine is unknown and hence it is not clear how nearly a free chlorine cation is involved.

Nitrogen heterocycles are not expected to be very susceptible to electrophilic attack, in the presence of Lewis Acids, for two reasons. First, localisation energy calculations show them to be intrinsically less susceptible to electrophilic attack than carbocyclic aromatic compounds. Secondly, they are themselves likely to complex with the catalyst to place a partial positive charge on the ring. Pyridine, for example, cannot be chlorinated with a ferric chloride catalyst,[18] although the same reagent readily chlorinates benzene. It has been shown,[18] that a complex is formed between pyridine and ferric chloride which is resistant to attack by the electrophile available.

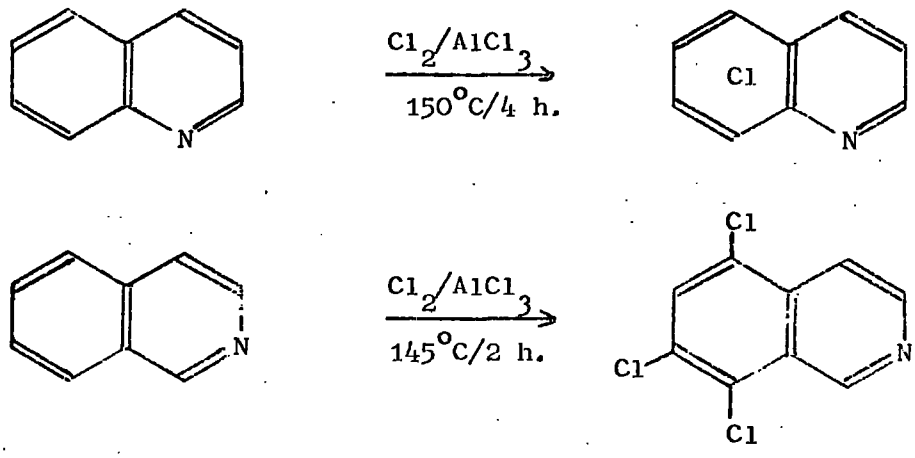


It is possible that the use of a more powerful Lewis Acid as catalyst, so that the electrophile is more nearly a free chlorine cation, would enable chlorination to proceed. This possibility has been demonstrated by the chlorination of pyridine in 50% yield at 100°C, with aluminium chloride as the catalyst.[18] Observations are consistent with the reaction proceeding in the following way.



The pyridinium salt produced is quite inactive towards the electrophile used so, when the mixture is hydrolysed at the end of the reaction, 3-chloropyridine and pyridine are recovered in equivalent amounts.

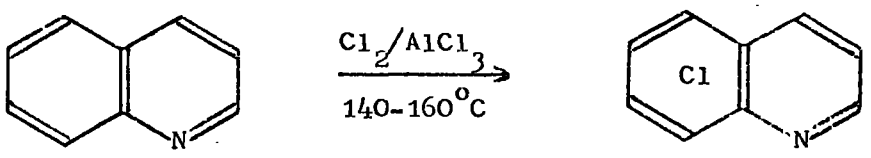
Quinoline and isoquinoline are much more susceptible to chlorination by chlorine with aluminium chloride as catalyst. Quite mild conditions lead to the production of 5,6,7,8-tetrachloroquinoline and 5,7,8-trichloroisoquinoline, respectively.[19]



This relatively easy chlorination occurs in the carbocyclic ring; presumably this is because any complexation through, or protonation of, the nitrogen atom, does not produce such a high positive charge on the carbocyclic ring as on the heterocyclic ring.

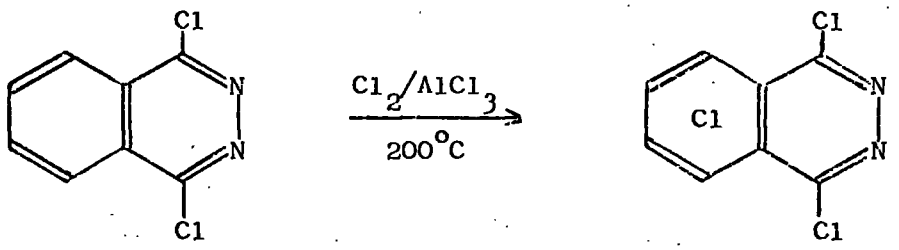
This chlorination method has become known as the 'swamping catalyst technique', because the aluminium chloride is used in equivalent, rather than truly catalytic, amounts. It has been developed by Chambers and co-workers, with rather more severe conditions, as one stage in the synthesis of a variety of perchlorinated heterocyclic compounds of nitrogen.

Normally, the carbocyclic ring, or rings, in the molecule is fully chlorinated by this technique, either before or after the heterocyclic ring has been chlorinated. Thus quinoline is converted to 5,6,7,8-tetrachloroquinoline in 87% yield, as the first step in the preparation of heptachloroquinoline.[20,21]

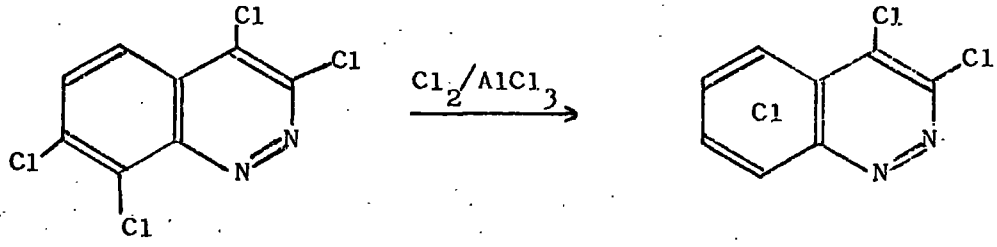


More vigorous conditions allowed the formation of some pentachloroquinoline, but the overall yield was decreased by polymerisation.

Hexachlorophthalazine is prepared from 1,4-dichlorophthalazine.[22]

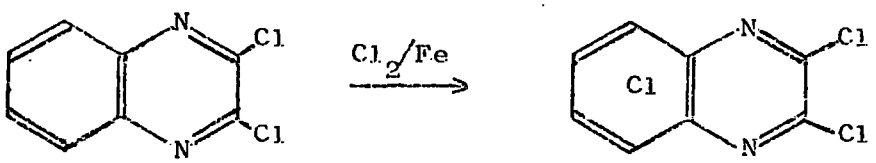


The reaction has also been used for the final stage of the preparation of hexachlorocinnoline.[23]



In the case of isoquinoline, aluminium chloride catalysed chlorination has been found to be sufficiently active to cause extensive substitution in the heterocyclic ring.[20] At 150°C, a single hexachlorisoquinoline was formed in 87% yield.

The quinoxaline nucleus seems to be sufficiently reactive for chlorination to occur with milder Lewis Acids as catalysts. Hexachloroquinoxaline has been obtained from 2,3-dichloroquinoxaline in this way.[24]



C. Chlorination by Compounds of Chlorine with Group V Elements

These reactions may be divided into those in which the chlorinating agent replaces hydrogen in the substrate, and those in which some other functional group, usually hydroxyl, is replaced.

As early as 1898, the chlorination of pyridine by phosphorus pentachloride in boiling phosphoryl chloride was attempted.[25] It was found that this method gave very little reaction, but that heating pyridine with dry phosphorus pentachloride in a sealed glass tube, at 210-220°C for 15 to 20h., produced a mixture containing a single dichloropyridine, three trichloropyridines, three tetrachloropyridines, pentachloropyridine, and other unidentified materials.

This method has been improved to provide a useful synthetic route to pentachloropyridine.[1] The main improvement was to use steel autoclaves which allowed the temperature to be increased to 285°C. Recovered di- and tri-chloropyridines were recycled so that a good yield of a mixture of pentachloropyridine and tetrachloropyridine was obtained. Separation of pentachloropyridine from this mixture was quite straightforward.

Phosphorus pentachloride has also been used to chlorinate aromatic and saturated hydrocarbons by stirring under dry nitrogen at temperatures up to 120°C.[26] Cyclohexane, n-heptane, toluene, mesitylene and cumene were all partially chlorinated in this way. It has been suggested that replacement of a hydrogen atom in a compound R-H occurs by the following mechanism.

$$PCl_5 \rightleftharpoons PCl_3 + Cl_2 \quad (1)$$

$$Cl_2 \rightleftharpoons 2\,Cl\cdot \quad (2)$$

$$Cl\cdot + RH \longrightarrow HCl + R\cdot \quad (3)$$

$$R\cdot + PCl_5 \longrightarrow RCl + \cdot PCl_4 \quad (4)$$

$$\cdot PCl_4 + RH \longrightarrow HPCl_4 + R\cdot \quad (5)$$

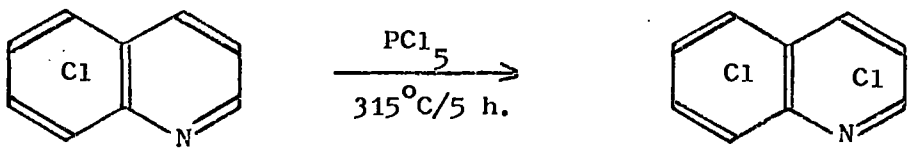
$$HPCl_4 \longrightarrow HCl + PCl_3 \quad (6)$$

$$\cdot PCl_4 \rightleftharpoons PCl_3 + Cl\cdot \quad (7)$$

Since the mechanism involves dissociation to phosphorus trichloride and chlorine, the chlorination is effectively achieved by elemental chlorine; phosphorus pentachloride acts simply as a convenient source of this. After reaction (4), the $\cdot PCl_4$ radical produced can react in two ways - with substrate or by dissociating. If the equilibrium (7) lies well to the right, then reactions (5) and (6) will be unimportant.

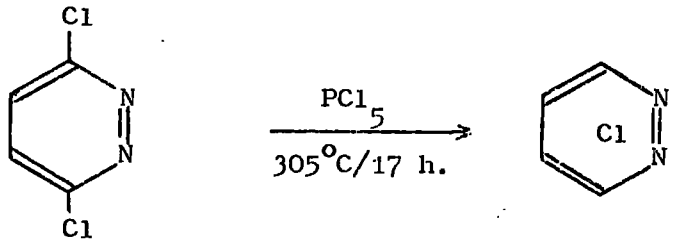
It is always found that the reaction of a nitrogen heterocycle with dry phosphorus pentachloride in an autoclave causes the heterocycle to be chlorinated, but this reaction is not always synthetically useful. Choice of substrate and conditions has to be made carefully if perchlorinated heterocyclic compounds of nitrogen are to be obtained.

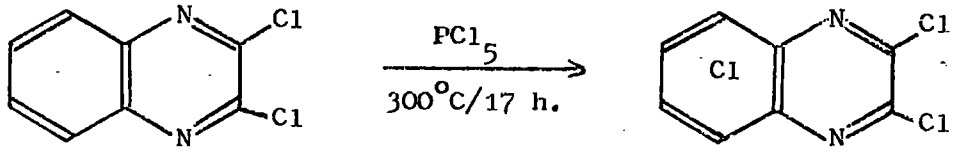
For example, the reaction between phosphorus pentachloride and quinoline at temperatures ranging from 250 to 285°C produces heptachloroquinoline, hexachloroquinoline and decomposition products.[27] This is not, however, a useful synthetic route to heptachloroquinoline, because of the great difficulty of separating the latter from the product mixture. Heptachloroquinoline is readily obtained by the chlorination of tetrachloroquinoline (prepared as in section (B) above) with phosphorus pentachloride.[20,28]

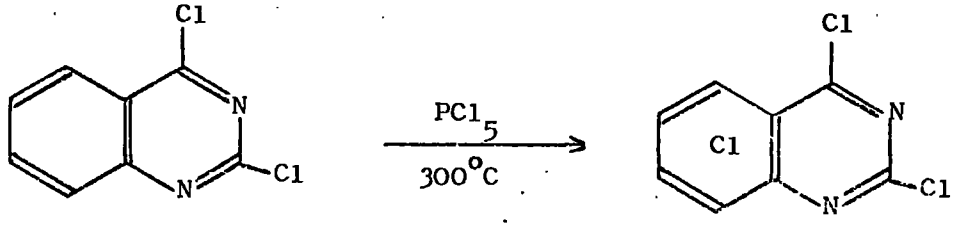


The five hours reaction time includes the time taken to heat the autoclave to the reaction temperature.

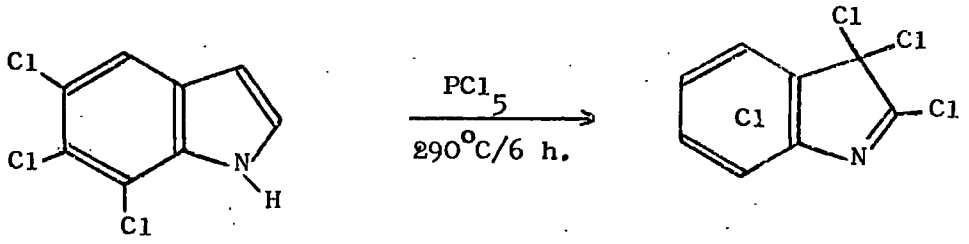
Phosphorus pentachloride has been quite frequently used to complete the chlorination of a heterocyclic nitrogen compound. Tetrachloropyridazine,[29] hexachloroquinoxaline,[30] and hexachloroquinazoline[31] are all synthesised by this kind of process.





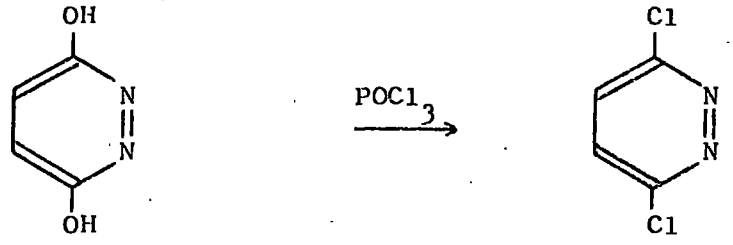


The chlorination of 5,6,7-trichloroindole with phosphorus pentachloride was originally thought to give heptachloroindole;[32] it has now been shown that the product is heptachloroindolenine.[33]

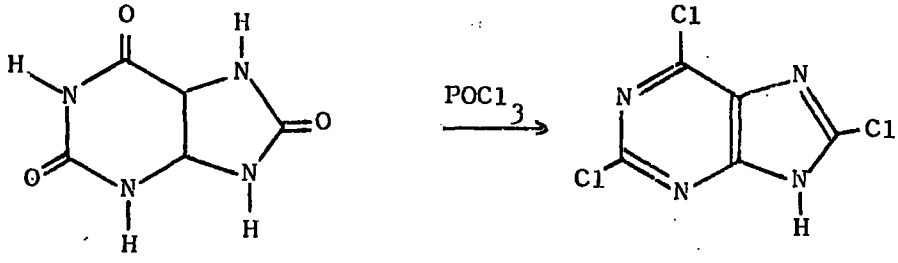


As mentioned before, compounds of the Group V elements are frequently used to replace hydroxyl groups by chlorine in a heterocyclic nitrogen compound. The reagent most frequently used is refluxing phosphoryl chloride; phosphorus pentachloride or dimethylaniline may be present and sometimes the reaction is achieved by phosphorus pentachloride alone.

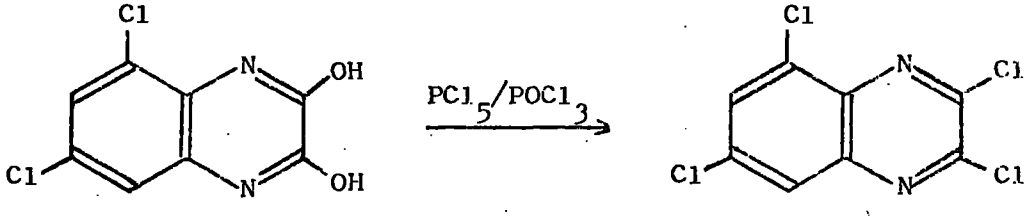
For example, 3,6-dihydroxypyridazine is converted to 3,6-dichloropyridazine by refluxing phosphoryl chloride alone.[34]



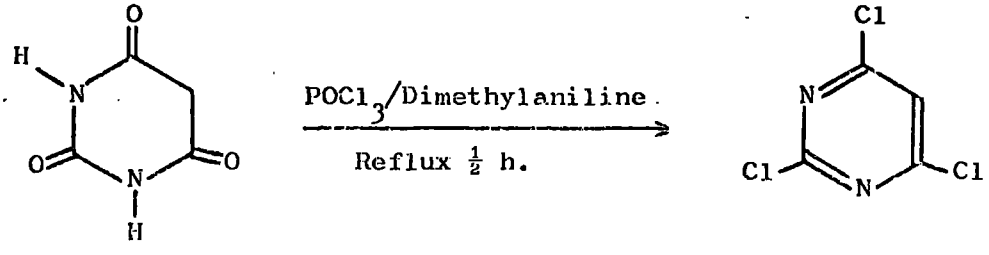
Uric acid is converted to 2,6,8-trichloropurine by boiling phosphoryl chloride alone.[35]

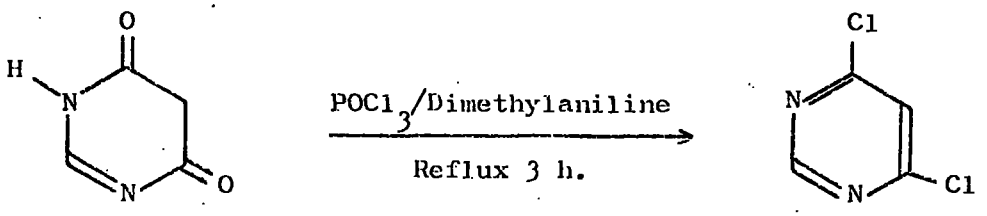


5,7-Dichloro-2,3-dihydroxyquinoxaline is converted to 2,3,5,7-tetrachloroquinoxaline by a mixture of phosphorus pentachloride and refluxing phosphoryl chloride.[24]

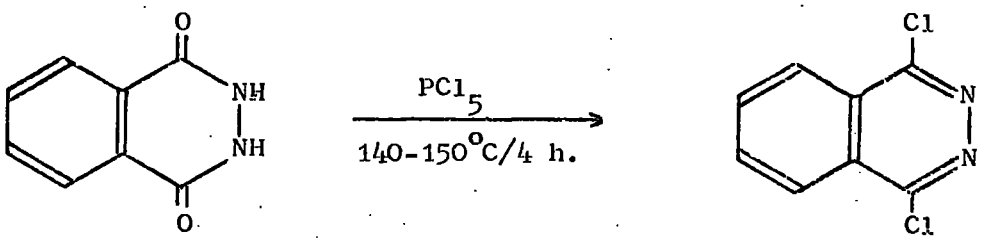


The keto tautomers of hydroxy compounds are also converted to the corresponding chloro compounds. Barbituric acid is converted to 2,4,6-trichloropyrimidine,[36] and 4,6-pyrimidindione is converted to 4,6-dichloropyrimidine,[37] by refluxing phosphoryl chloride and a little dimethylaniline.

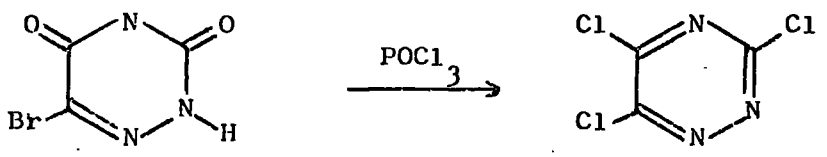




In some cases, considerable care must be taken in choice of conditions, to obtain an efficient reaction. For example, quite a lot of work has been done on the synthesis of 1,4-dichlorophthalazine from 1,4-dioxophthalazine. Some workers have described reactions using phosphoryl chloride as reagent,[38,39] while others have described reactions using phosphorus pentachloride as reagent.[40-42] Much more recently, Hirsch and Orphanos have claimed that none of these methods are really satisfactory for obtaining pure 1,4-dichlorophthalazine.[43] They believe they have devised a better reaction using phosphorus pentachloride in a sealed system.



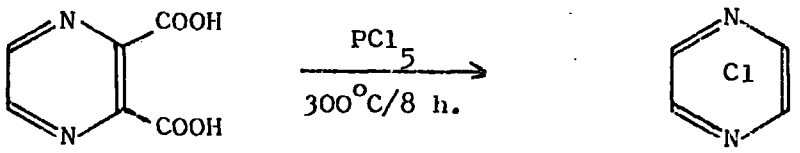
The value of including phosphorus pentachloride and alkylated anilines is seen in the preparation of trichloro-1,3,4-triazine. This was first isolated pure by the reaction of phosphoryl chloride alone on 5-bromo-6-azauracil.[44]



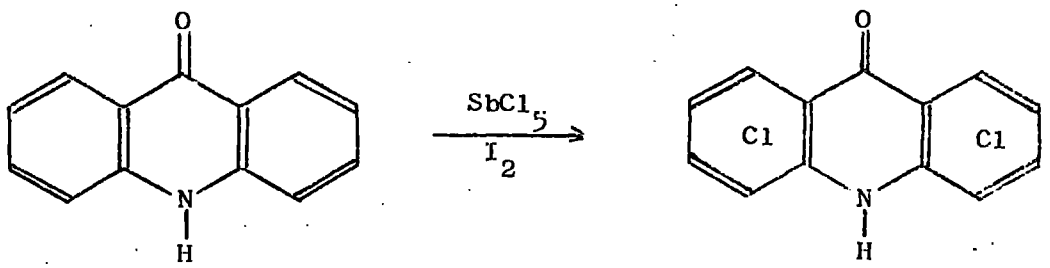
It has since been shown[45] that the yields are improved by the addition of phosphorus pentachloride and N,N-diethylaniline.

As well as replacing hydroxyl and keto groups, phosphorus pentachloride has been used to replace carboxylic acid groups by chlorine. For example,

tetrachloropyrazine may be prepared from pyrazine-2,3-dicarboxylic acid by reaction with phosphorus pentachloride in an autoclave.[46]



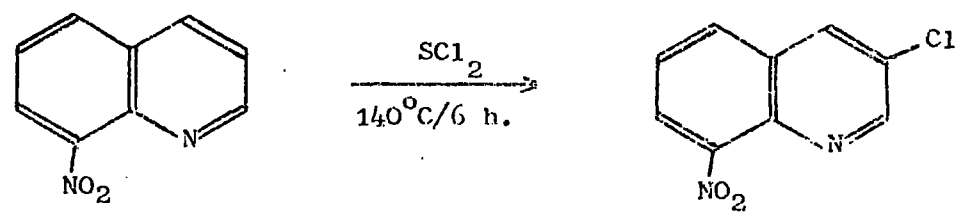
Of the other Group V elements, only antimony has been used in its compounds to achieve chlorination of heterocyclic compounds. Antimony pentachloride is known to be a vigorous chlorinating agent and in 1882 it was shown that, when quinoline is heated with antimony pentachloride at temperatures ranging from 170-400°C, hexachlorobenzene and hexachloroethane are produced.[47] A more synthetically useful reaction is the conversion of 9-acridanone to octachloro-9-acridanone by antimony pentachloride and iodine catalyst, which was reported in 1914.[48]



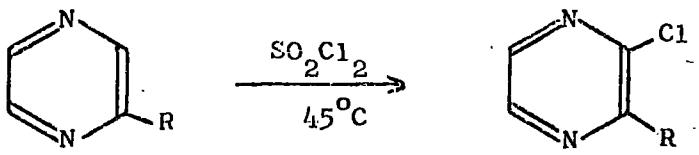
No reaction conditions were specified and this report does not seem to have been followed up.

D. Chlorination By Other Chlorinating Reagents

Compounds of sulphur are quite frequently used as chlorinating agents. Simple compounds are not very active; sulphur dichloride, for example will only chlorinate 8-nitroquinoline to 3-chloro-8-nitroquinoline.[49]

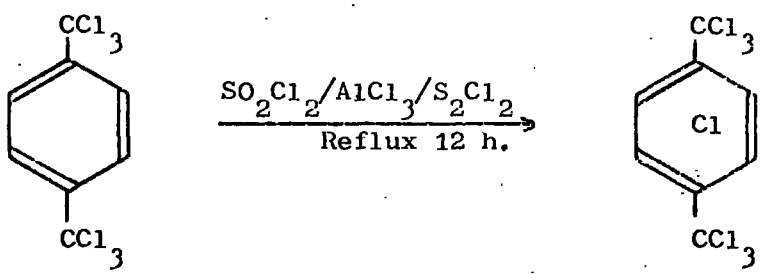


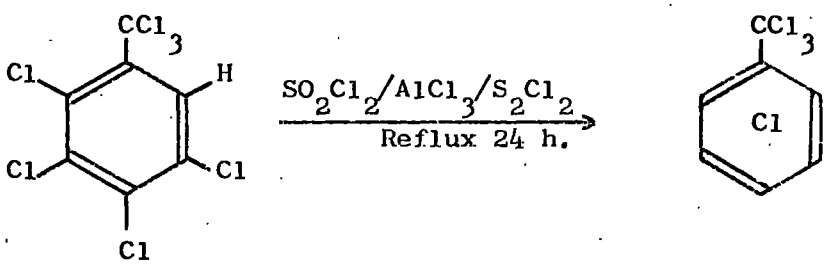
Sulphuryl chloride, in solution in N,N-dimethylformamide has been shown to be a general reagent for chlorinating 2-alkylpyrazines in the 3-position.[50]



In 1922, Silberrad reported that a mixture of sulphur monochloride, aluminium chloride and sulphuryl chloride produced a very potent chlorinating reagent in sulphuryl chloride solution.[51] He postulated that the chlorinating agent formed was $Al_2S_2Cl_8$ and, by varying reagent concentrations and the temperature, he was able to chlorinate benzene to almost any desired degree, including complete conversion to hexachlorobenzene.

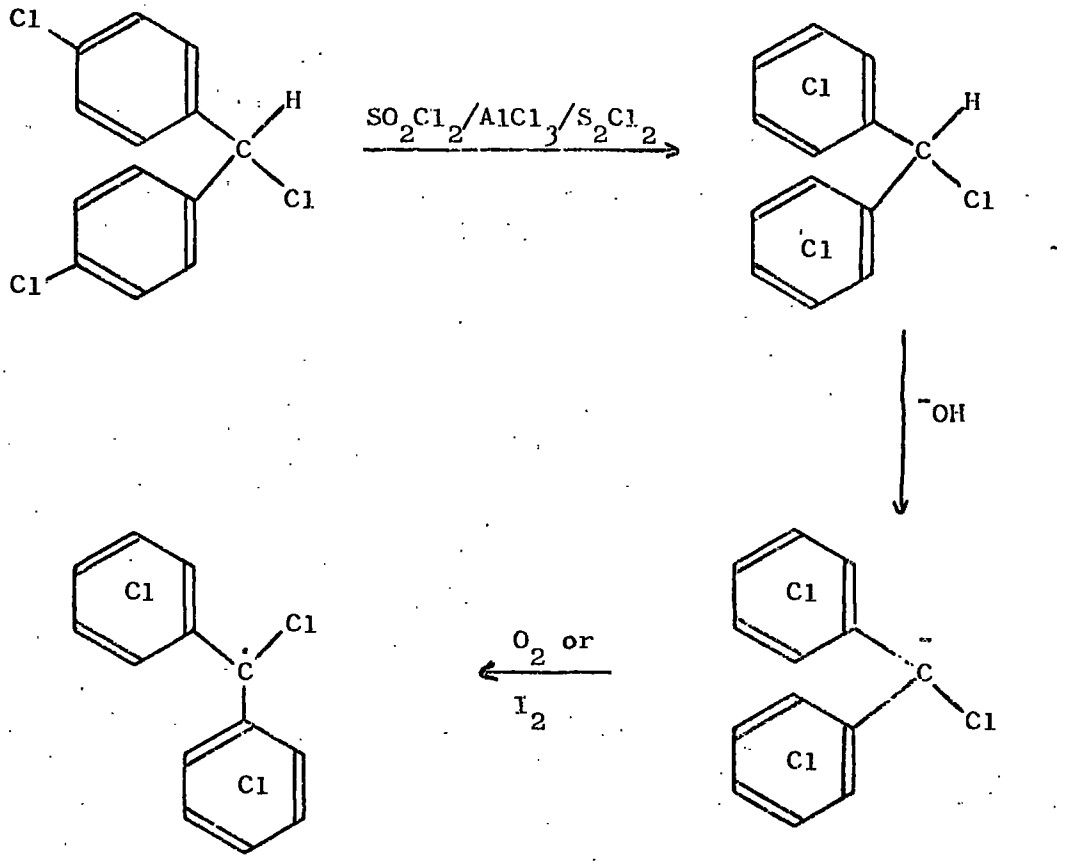
This work was not extended until 1960 when Ballester, Mollinet and Castaner[52] adapted the reagent by using greater amounts of aluminium chloride and sulphur monochloride. They were able to obtain highly chlorinated alkyl aromatic compounds, including decachloro-para-xylene and octachlorotoluene.





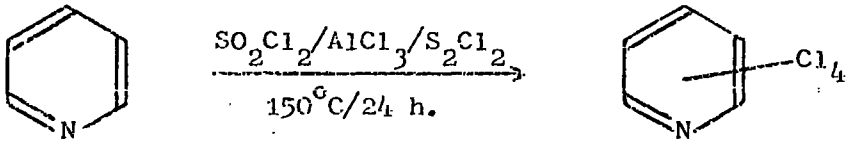
This Silberrad-BMC reagent (after the workers who devised and developed it) has been widely used for a wide variety of chlorinations. Recently the

undecachlorodiphenylmethyl radical has been made using the reagent for a chlorination step.[53]

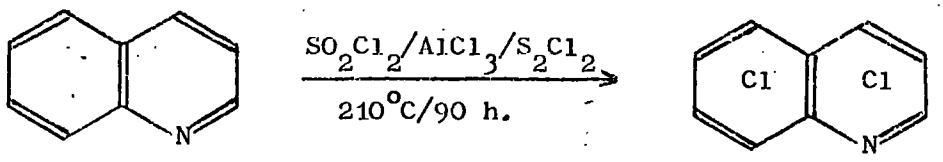


So far, no perchlorinated heterocyclic nitrogen compound has been synthesised using this reagent, but there have been some preliminary investigations on the use of the reagent for chlorinating heterocyclic compounds.

Pyridine and quinoline are found to be much less susceptible to chlorination by this reagent than is benzene,[54] confirming that the process is electrophilic. Neither of these compounds was significantly chlorinated, unless the reaction was carried out at a high temperature, under pressure in an autoclave. Under these conditions, tetrachloropyridine can be obtained from pyridine.

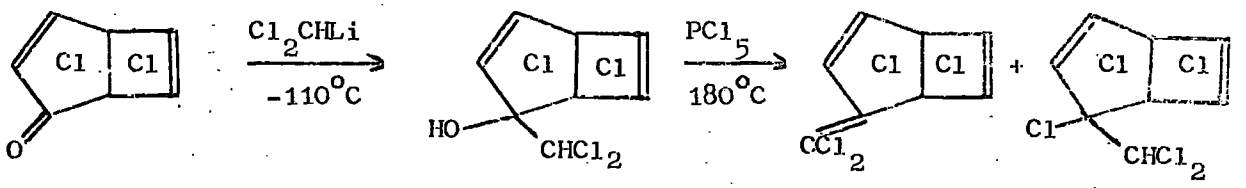


Under very forcing conditions, heptachloroquinoline may be obtained from quinoline.

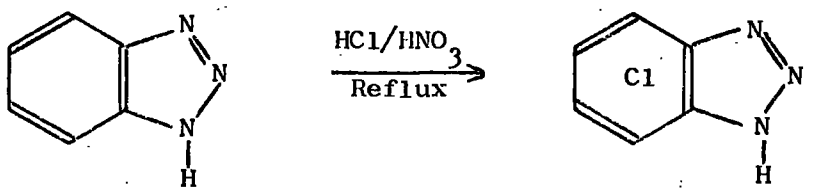


As the yield is only 7% and separation from decomposition products is difficult, this is not a synthetically useful reaction.

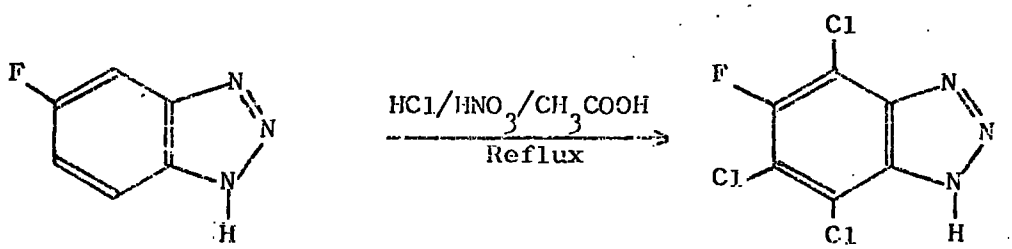
A chlorinating reagent with a rather specialised use is dichloromethyl lithium and phosphorus pentachloride. It has not been applied to heterocyclic systems but, in carbocyclic systems, it has been shown to replace a carbonyl group by a dichloromethylene group.[55]



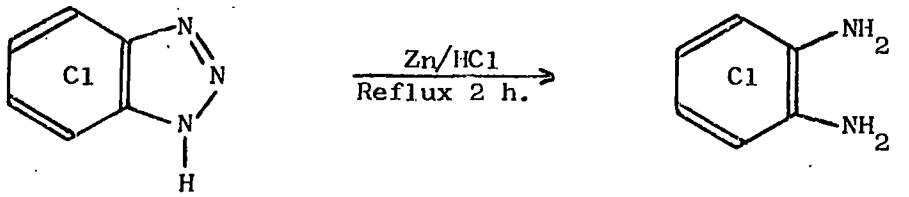
There is another chlorination agent which has a specialised use for the benzotriazole ring system. Refluxing aqua regia converts this system to 4,5,6,7-tetrachlorobenzotriazole.[56]

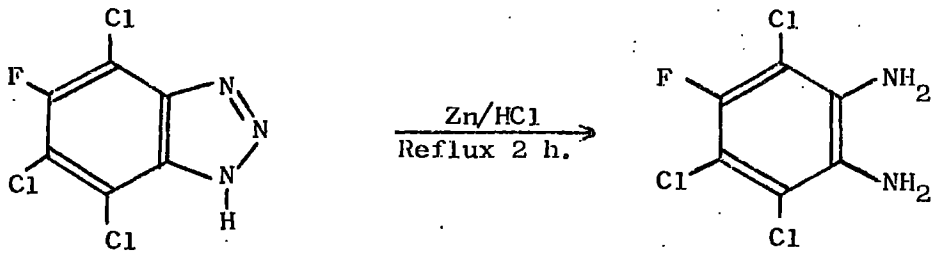


This reaction has been shown to be generally applicable to benzotriazole derivatives, if acetic acid is added to the mixture.[57] For example, 4,6,7-trichloro-5-fluorobenzotriazole is prepared from 5-fluorobenzotriazole.



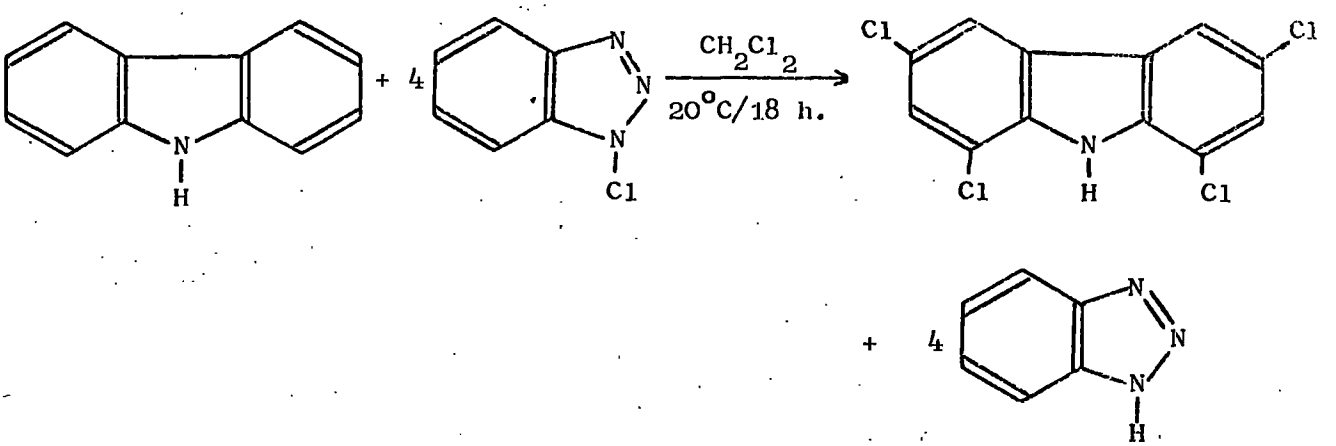
The preparation of these benzotriazoles is important because they are converted to the corresponding orthophenylenediamines by zinc in hydrochloric acid.[57]





The orthophenylenediamines are important as starting materials for synthesising more complex ring systems by cyclisation.

1-Chlorobenzotriazole has been used as a chlorinating agent for various carbazole derivatives.[58] As many as four chlorine atoms have been substituted in the carbazole ring.

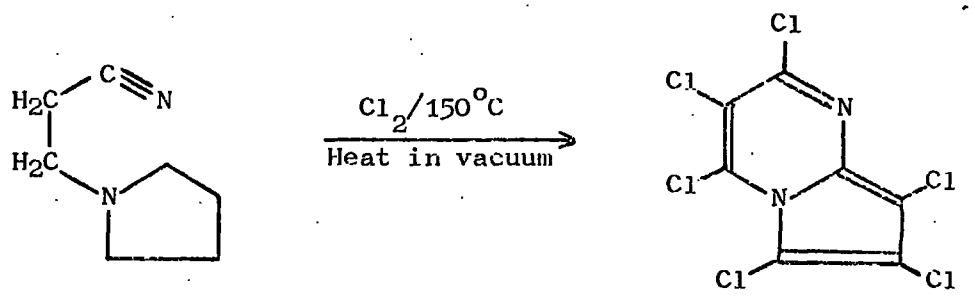


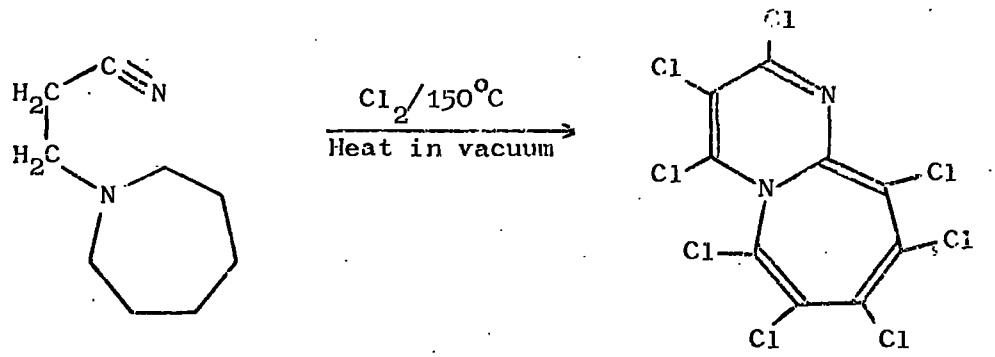
2.2 Methods Involving Cyclisation

Any system of classifying these reactions is bound to be somewhat arbitrary. The one used here is based on convenience, rather than on any theoretical or mechanistic distinctions.

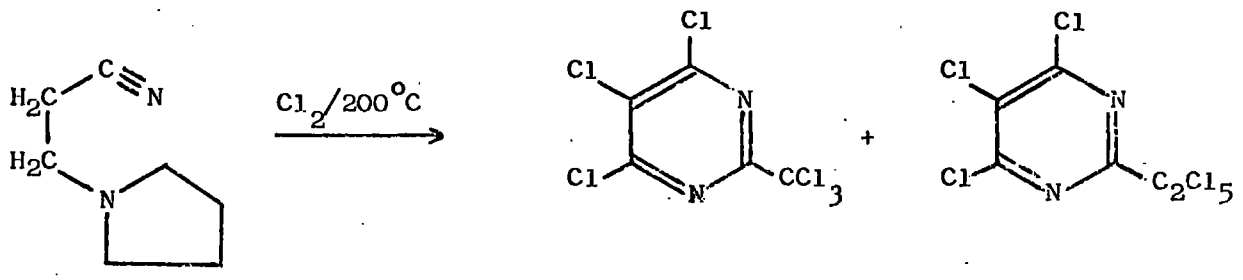
A. Reaction Where Chlorinating Agents Cause Cyclisation

Beck and co-workers have investigated chlorination reactions of cyanoalkylated secondary amines,[59] and found two types of reaction depending on the conditions. Chlorination at fairly low temperatures, followed by vacuum pyrolysis, gives the fused pyrimidines shown below in a reaction involving chlorination and cyclisation.



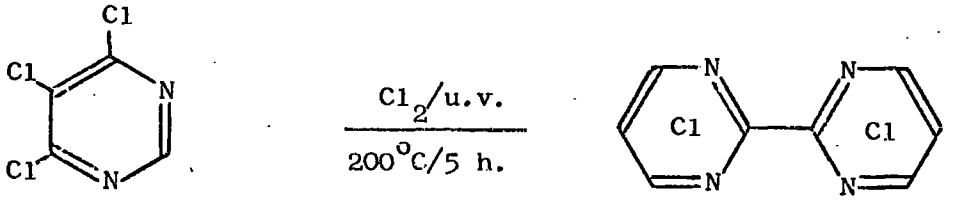


However, for the first compound, chlorination at a higher temperature involves chlorination, cyclisation, and loss of a methane or an ethane fragment so that alkyl pyrimidines are produced.

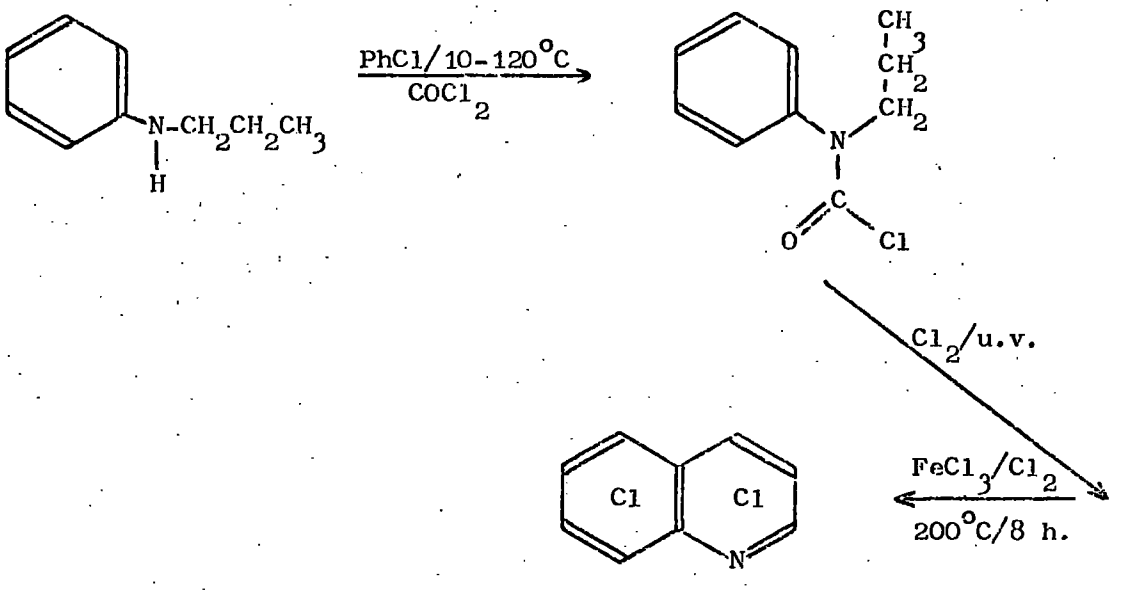


When the chlorination of 4,5,6-trichloropyrimidine is attempted under ultra-violet irradiation, no more chlorine is introduced but coupling of two

pyrimidine units together occurs.[60]

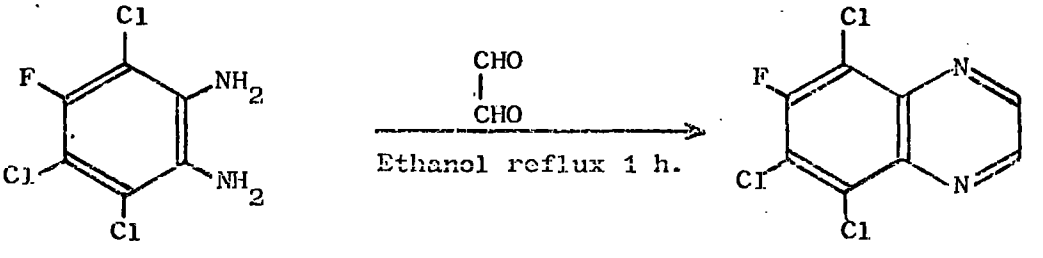


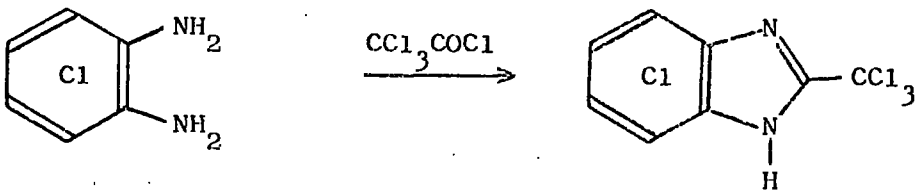
A cyclisation of seondary amines has also been used to prepare heptachloroquinoline.[61] Thus the chlorination of n-propylphenylamine under increasingly severe conditions leads to heptachloroquinoline.



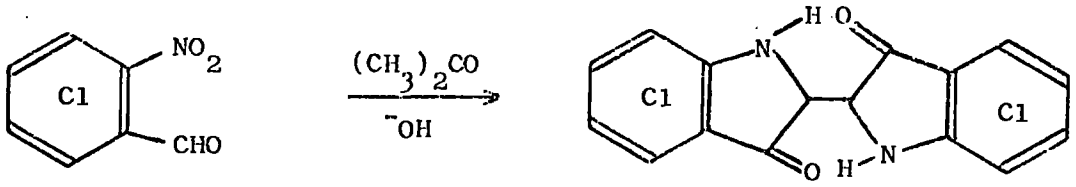
B. Reactions of Tetrachloro-orthophenylene Derivatives and Similar Compounds

As mentioned in section 2.1.D above, tetrachloro-orthophenylene diamine and its derivatives are readily available from benzotriazoles. The amine functions will react with carbonyl compounds and this reaction has been used to achieve cyclisation.[57] In this way, 4,6,7-trichloro-5-fluoroquinoxaline and 4,5,6,7-tetrachloro-2-trichloromethylbenzimidazole[62] have been prepared.

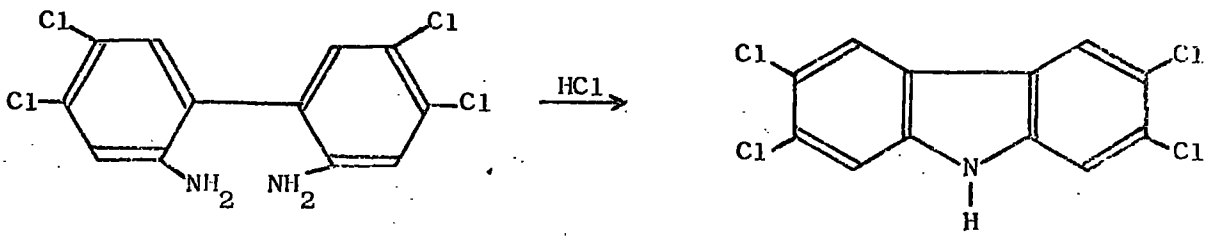




Another tetrachloro-orthophenylene compound to have been cyclised is tetrachloro-2-nitrobenzaldehyde which, on treatment with acetone in alkaline solutions produces an indigo type compound.[63,64]



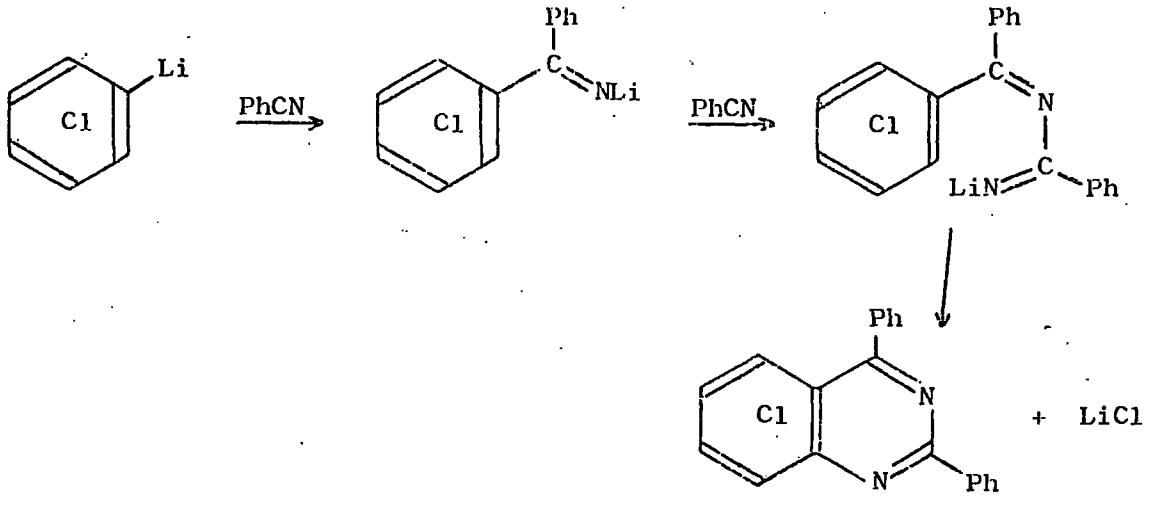
Another cyclisation reaction involving a diamine, but not an ortho-phenylene diamine, is the preparation of a carbazole from a 2,2'-diamino-biphenyl by the action of acid.[65]



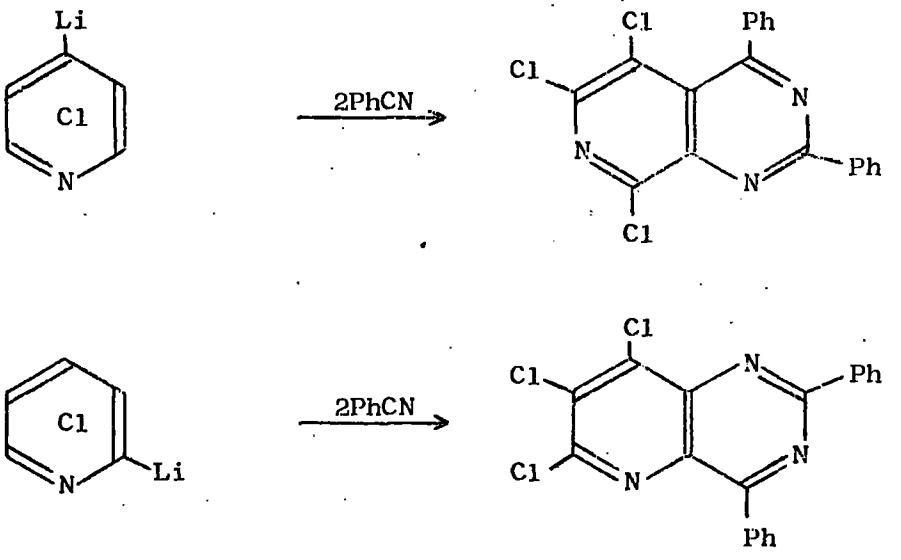
C. Reactions Involving Nitriles

These reactions are normally with perchloroaryl lithiums; Wakefield and coworkers have investigated the reaction of a wide range of nitrilic compounds with pentachlorophenyl lithium.[66,67] They have prepared 2,4-diaryl-5,6,7,8-tetrachloroquinazolines by reaction of two moles of the aryl nitrile with pentachlorophenyl lithium, in diethyl ether at -20°C, followed

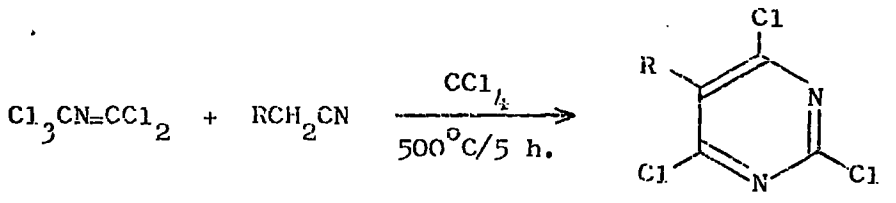
by refluxing for three hours. For example:



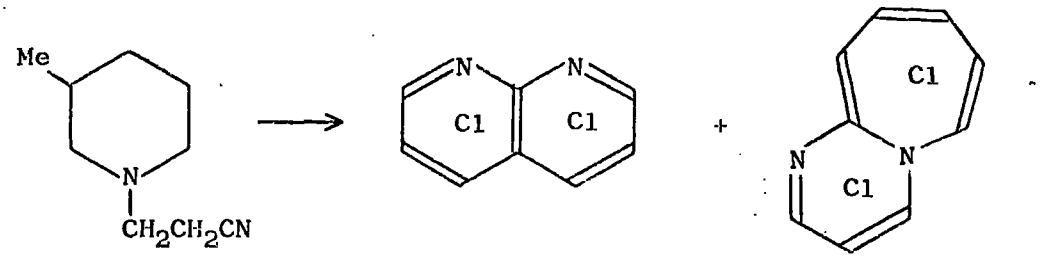
The same workers have also studied the reactions of tetrachloropyridyl lithiums with benzonitrile.[68] Thus tetrachloro-4-pyridyl lithium reacts giving 5,6,8-trichloro-2,4-diphenyl-1,3,7-triazanaphthalene, while tetrachloro-2-pyridyl lithium reacts giving 6,7,8-trichloro-2,4-diphenyl-1,3,5-triazanaphthalene.



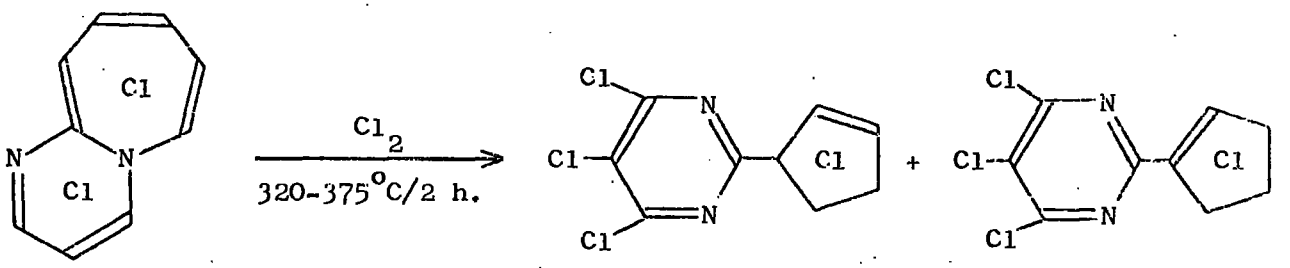
A quite general synthesis of 2,4,6-trichloropyrimidines has been found to be the reaction of dichloroisocyanides with nitriles containing a methylene group next to the nitrile function.[69]



Chlorination of N-cyanoalkylpiperidines has been found to lead to an interesting cyclisation.[70] Chlorination in chloroform at 25-35°C is followed by exhaustive chlorination at 300°C and octachloropyrimido[1,2-a] azepine and 2,3,4,5,6,7-hexachloro-1,8-naphthyridine are obtained in low yield.



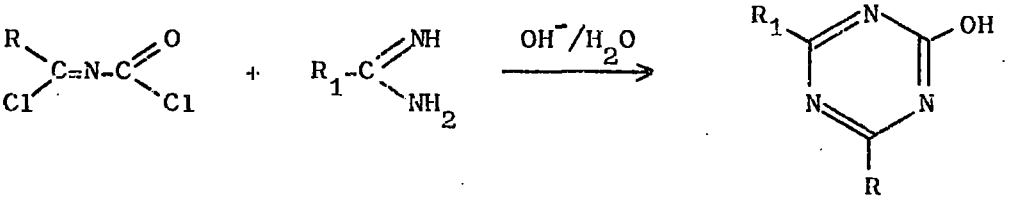
The pyrimido azepine rearranges to pyrimidine derivatives if it is chlorinated further.[71]



D. Reactions Involving Other Multiple Carbon to Nitrogen Bonds

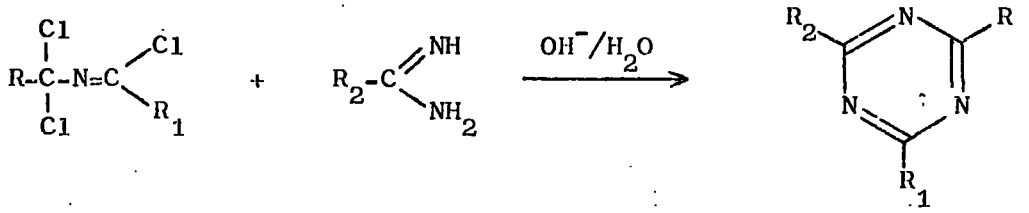
Holtschmidt and coworkers have shown that isocyanates with a dichloromethylene group adjacent to the isocyanate function exist extensively as carbamoyl chlorides.[72]

In this form, these compounds will react with various amidines to give triazines.[73]



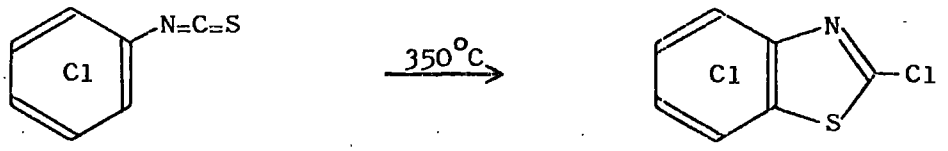
The nature of the R groups is quite critical to the success of the reaction. R normally has to be phenyl or trichloromethyl, but R_1 may be much more variable and could be a chlorine atom.

Amidines will also react with polychloroaza-alkenes to give triazines.[73]

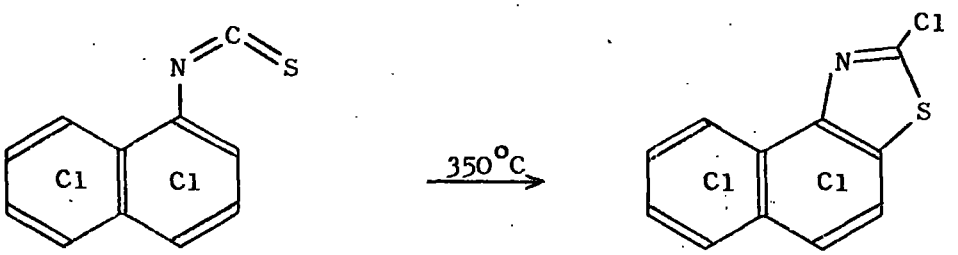


R, R_1 and R_2 may all be quite extensively varied and can be chlorine atoms or chlorinated alkyl or aryl groups.

The same workers have studied the reactions of isothiocyanates. They find that pentachlorobenzothiazole is formed by heating pentachlorophenyl-isothiocyanate at 350°C.[74]

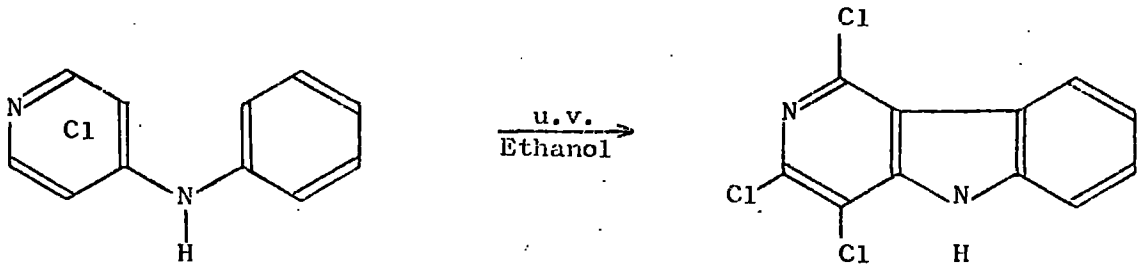


Heptachloronaphtho[1,2-d]thiazole is similarly formed from heptachloro-naphthalene-1-isothiocyanate.[74]

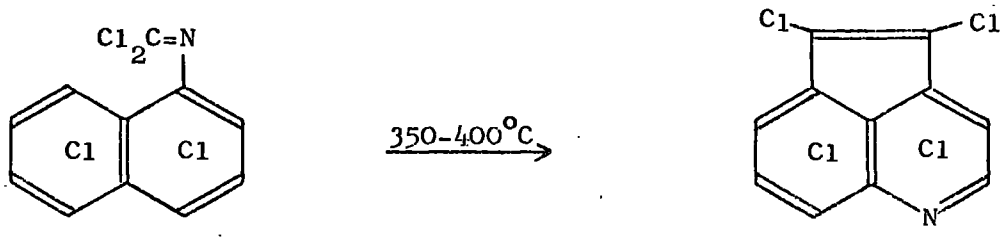


E. Pyrolysis and Photolysis Reactions

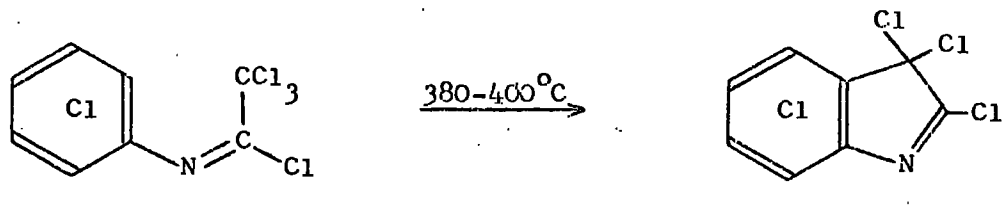
The irradiation of tetrachloro-4-N-anilino pyridine in ethanol solution has been shown to produce 3-aza-1,2,4-trichlorocarbazole.[75]



5-Azaheptachloro-acenaphthylene is produced, in an interesting reaction where cyclisation is accompanied by rearrangement, by heating heptachloro-naphthalene-1-isocyanide dichloride, under argon in a sealed system.[76]

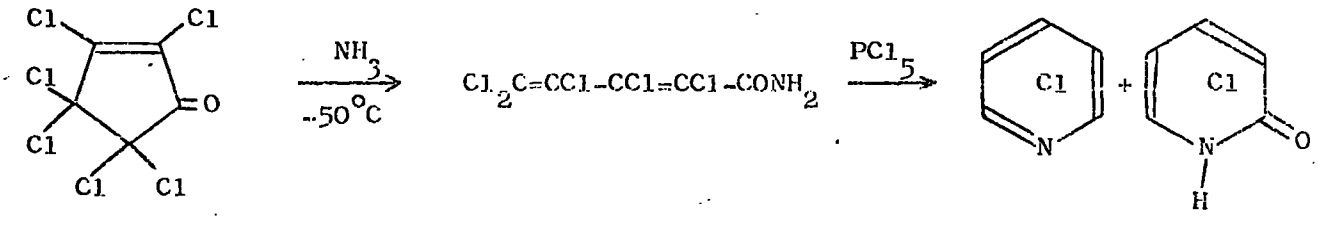


The indole ring system has also been obtained by thermal cyclisation of a suitable isocyanide derivative. Heptachloroindolenine has been prepared in this way by passing the reagent through the apparatus in a slow stream of nitrogen.[77]

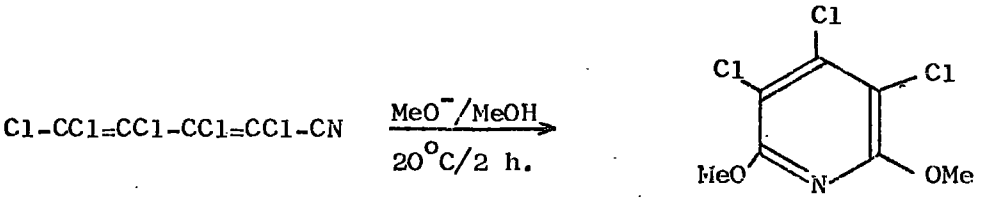


F. Miscellaneous Reactions

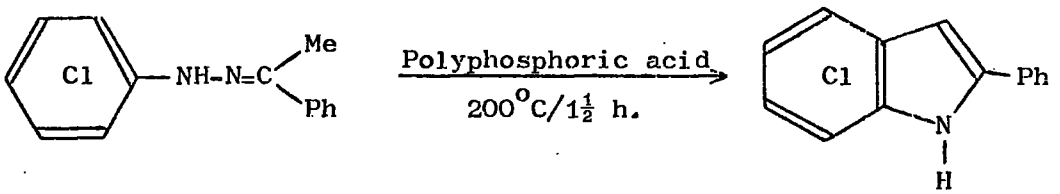
The pyridine ring system has been synthesised starting from hexachloro-cyclopenten-3-one.[78] Reaction with liquid ammonia in diethyl ether produces an acyclic amide which, on further treatment with phosphorus pentachloride gives a mixture of tetrachloro-2-pyridone and pentachloropyridine.



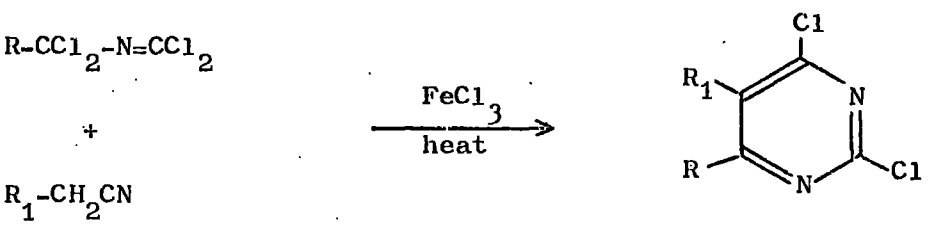
The pyridine ring system is also obtained from chlorinated, unsaturated nitriles by reaction with alkoxides.[79] A wide range of alkoxides has been used to prepare 2,6-dialkoxy-3,4,5-trichloropyridines. For example, 3,4,5-trichloro-2,6-dimethoxypyridine has been prepared by using methoxide ion in methanol.



There is a synthesis of 4,5,6,7-tetrachloroindoles based on pentachlorophenylhydrazones.[80] The latter are prepared from the appropriate ketone and pentachlorophenylhydrazine. Unfortunately, this synthesis is not completely general, but it has been used to prepare 4,5,6,7-tetrachloro-2-phenylindole, with polyphosphoric acid as the cyclising agent.



2,4-Dichloropyrimidines have been prepared starting from an isocyanide dichloride and a nitrile, in a reaction which is catalysed by Lewis Acids.[81]



For the yields to be significant, R has to be a chlorine atom, but the identity of R_1 may be quite widely varied.

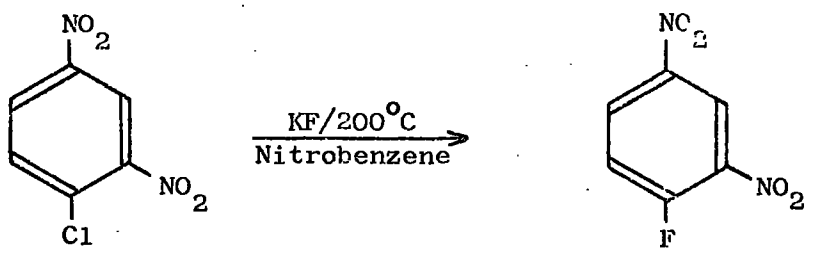
3. Reactions of Perchloroheteroaromatic Compounds Containing Nitrogen

3.1 Conversion to Corresponding Perfluoroheteroaromatic Compounds

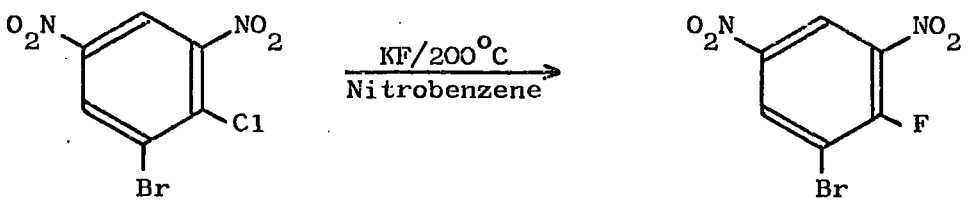
The most general and successful method for achieving this reaction,

known as a halogen exchange reaction, is to use a metal fluoride, either in a solvent, or in the solid phase. The use of halogen exchange reactions in the preparation of fluorinated organic compounds has been reviewed, and the review includes sections on halogen exchange in aromatic and hetero-aromatic compounds.[82] Experiments on the solid phase fluorination of chloro-2,4-dinitrobenzene with several different metal fluorides have shown that caesium fluoride is the most reactive metal fluoride, followed quite closely by potassium fluoride,[83,84] which is the reagent most commonly used.

Since the reactions are essentially nucleophilic displacements in an aromatic system, some activating group would be expected to be necessary and the earliest halogen exchange reaction reported was in chloro-2,4-dinitrobenzene, which is highly activated, in nitrobenzene solution.[85]



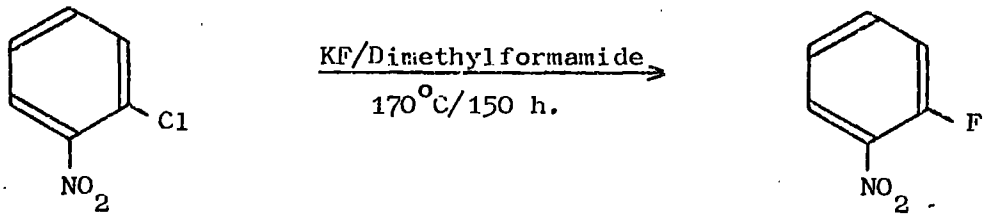
Other dinitrobenzenes, such as 1-bromo-2-chloro-3,5-dinitrobenzene, have been shown to undergo halogen exchange in nitrobenzene solution, but mononitro-benzenes, such as 1,3-dibromo-2-chloro-5-nitrobenzene, will not react.

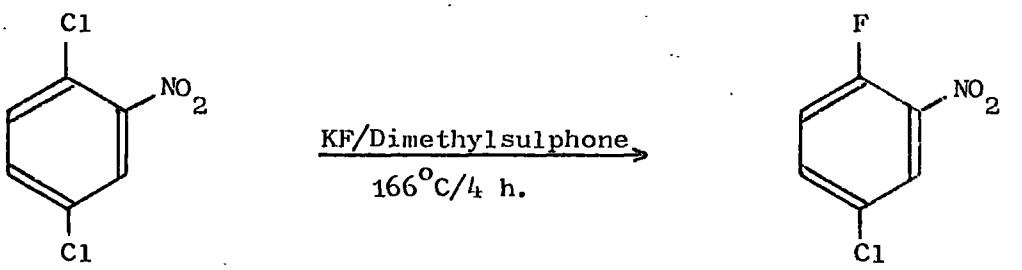


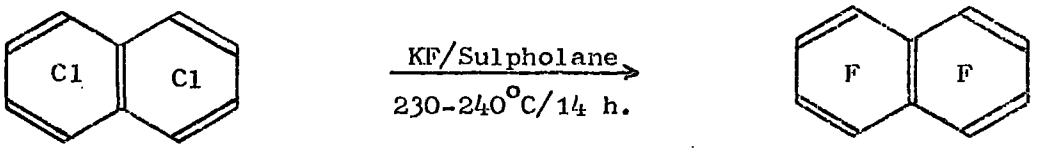
The use of more polar, aprotic solvents, such as N,N-dimethylformamide, dimethylsulphone, N-methyl-2-pyrrolidone, and sulpholane, has allowed halogen exchange reactions to be achieved on less activated systems.

For example, 2-chloronitrobenzene is converted to 2-fluoronitrobenzene in N,N-dimethylformamide;[87] 1,4-dichloro-2-nitrobenzene is converted to

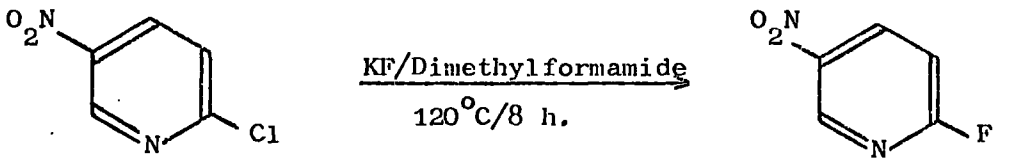
1-chloro-4-fluoro-3-nitrobenzene in dimethylsulphone;[88] and octachloronaphthalene is converted completely to octafluoronaphthalene in sulpholane.[89]



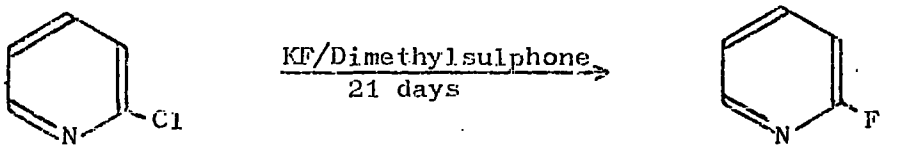




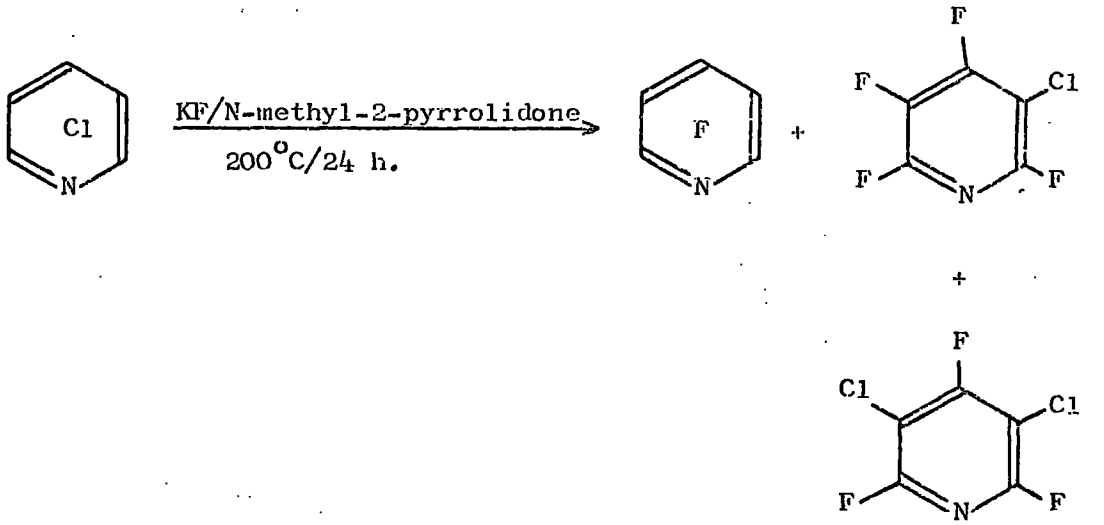
Heterocyclic nitrogen compounds, too, will undergo halogen exchange in various solvents, but some activating group other than the ring nitrogen atom is sometimes necessary. Thus 2-chloro-5-nitropyridine is converted to 2-fluoro-5-nitropyridine by potassium fluoride in N,N-dimethylformamide, but 2-chloropyridine is unaffected by this reagent.[90]



Using dimethylsulphone or sulpholane, however, it was possible to replace the chlorine atoms in simple chloropyridines, but rather long reaction times were necessary.[91]

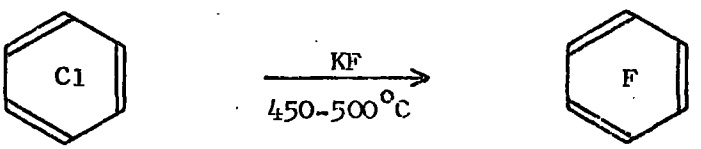


Using N-methyl-2-pyrrolidone as the solvent, a mixture of pentafluoropyridine, 3-chlorotetrafluoropyridine, and 3,5-dichlorotrifluoropyridine has been obtained from pentachloropyridine.[92]

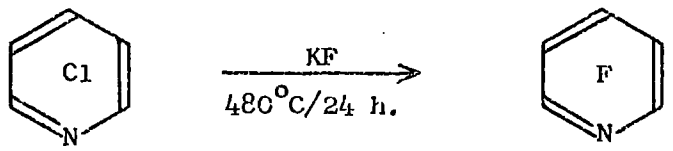


The preparation of octafluoronaphthalene,[89] is the only preparation of a fully fluorinated aromatic or heteroaromatic system, by halogen exchange in a solvent which has been reported and it has not been possible to prepare hexafluorobenzene from hexachlorobenzene by this technique. Probably this is because the solvents cannot be used at temperatures as high as those which are needed.

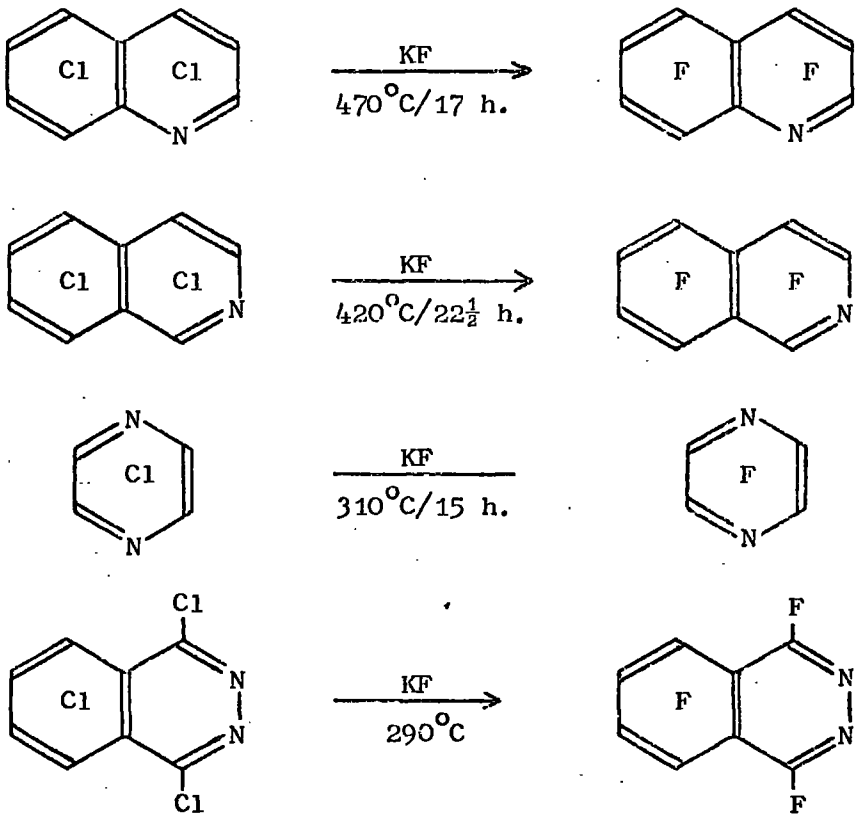
Reaction of hexachlorobenzene with solid potassium fluoride in an autoclave, however, produces hexafluorobenzene, with other less fully fluorinated products,[93] and hexafluorobenzene may be obtained pure by distillation.



In the field of heterocyclic nitrogen chemistry, potassium fluoride in the solid phase was first used for the synthesis of pentafluoropyridine from pentachloropyridine.[1,92]



This solid phase halogen-exchange reaction has been shown to be fairly generally applicable to the conversion of perchloroheterocyclic nitrogen compounds to the corresponding perfluoroheterocycles. For example, heptafluoroquinoline,[20,94] heptafluoroisoquinoline,[20] tetrafluoropyrazine,[46] and hexafluorophthalazine[22] have all been synthesised in this way.



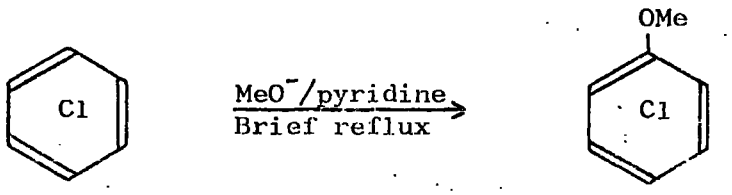
In all of these reactions, the material isolated from the autoclave contains some uncompletely fluorinated substances, but the perfluoroheterocyclic compound may be obtained pure by distillation. The temperature of the reaction is highly critical in the preparation of hexafluorophthalazine because, if it is much higher than 290°C, extensive decomposition occurs while, if it is much lower than 290°C, then fluorination is not nearly

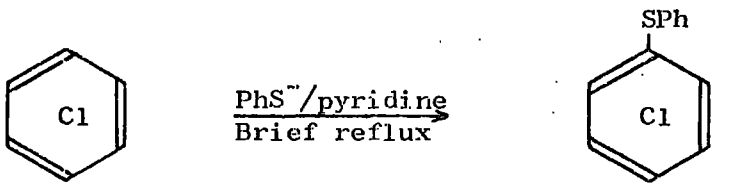
completed. It is apparent that complicating side reactions can occur and that the fluorination of other perchlorinated systems by this method may present considerable difficulties.

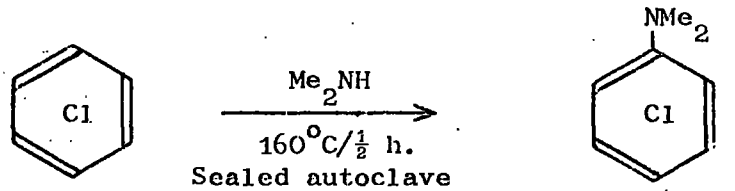
3.2 Nucleophilic Substitution Reactions

A. Chlorinated Carbocyclic Aromatic Compounds

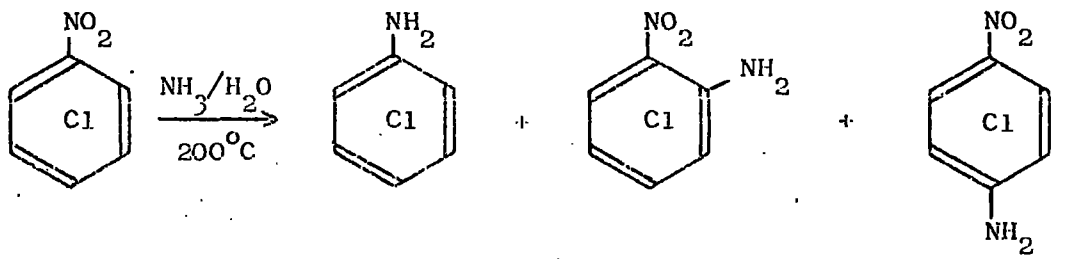
(i) Chlorobenzenes. Hexachlorobenzene has been known to be a quite inert compound for a long time but it has more recently been shown to undergo nucleophilic substitution, and especially readily if pyridine is used as solvent.[95] Some of the reactions which have been observed are shown below.



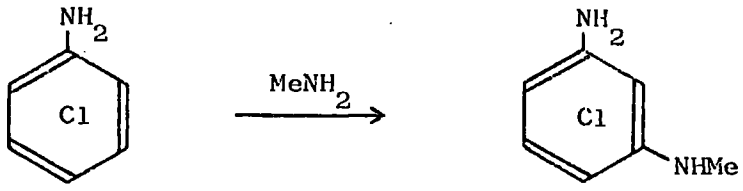


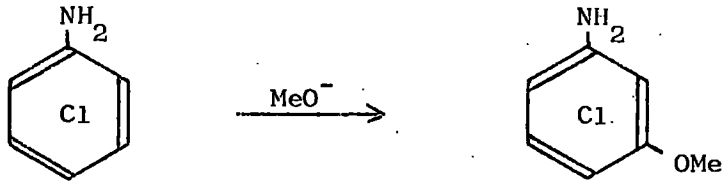


The orientation of disubstitution seems to be quite variable and is further complicated by the tendency of the first substituent to be replaced, rather than chlorine. For example, pentachloronitrobenzene reacts with aqueous ammonia to replace the nitro group, or to give ortho or para substitution, with the replacement of the substituent accounting for 60% of the reaction.[96]

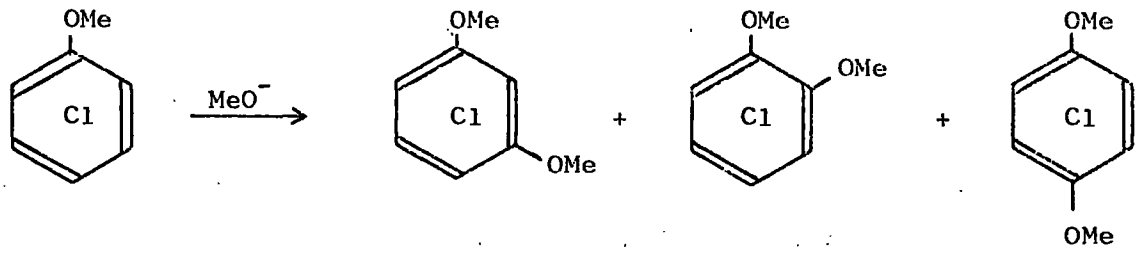


Pentachloroaniline, however, gives exclusively meta substitution with methylamine[96] or with methoxide ion.[97]

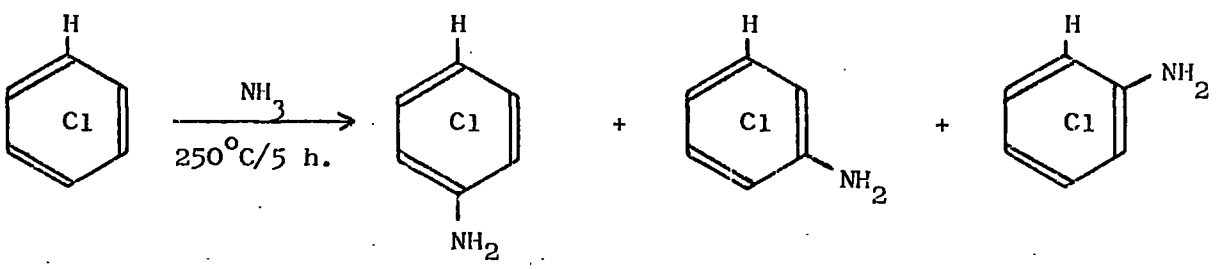


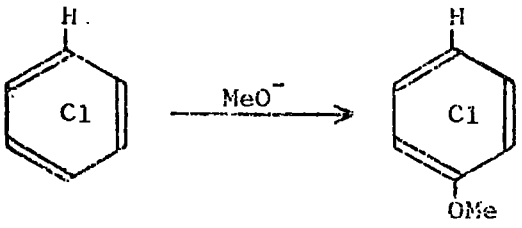


Reaction of methoxide ion with pentachloroanisole produces some of all three possible disubstituted products.[97]

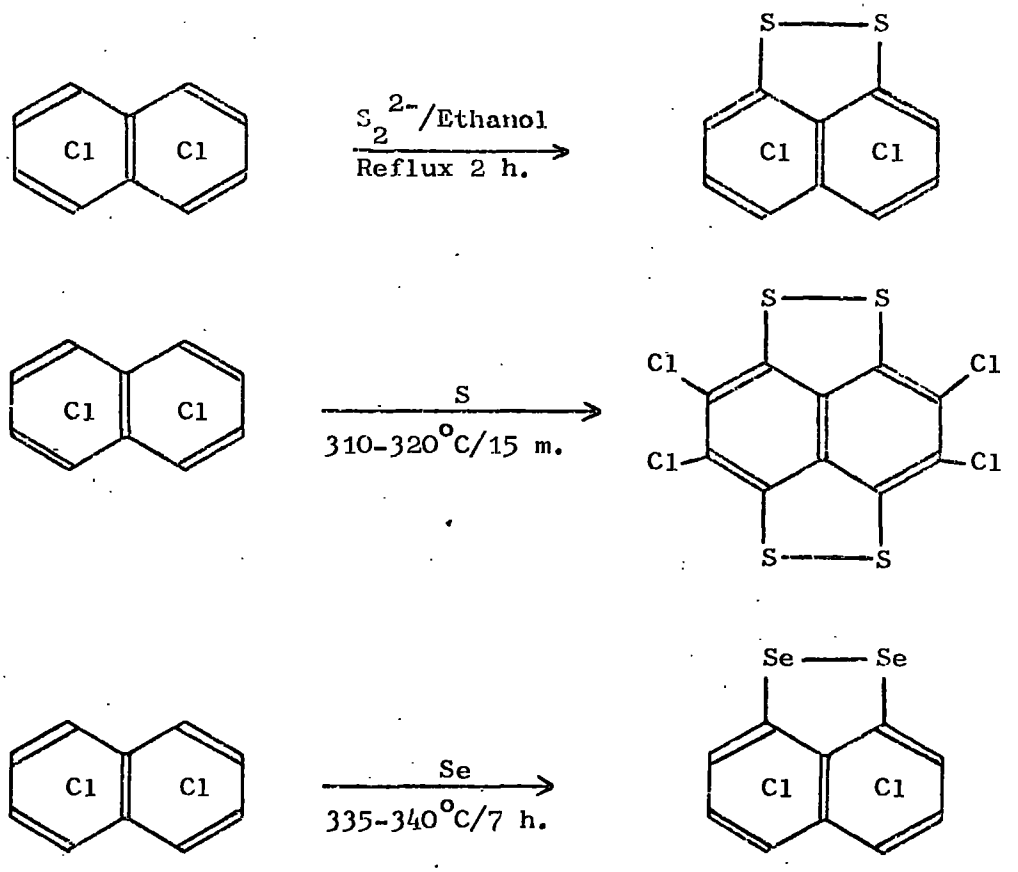


The orientation of substitution in pentachlorobenzene is particularly interesting, if rationalisations of orientation patterns are to be made. With a range of nucleophiles, substitution of pentachlorobenzene occurs mainly in the para position with ammonia giving 52% para substitution,[98] and methoxide ion giving almost exclusive para substitution.[99]





(ii) Chloronaphthalenes. The reactions of octachloronaphthalene have not been very thoroughly examined but, like hexachlorobenzene, it seems to be quite resistant to nucleophilic attack, and the only reactions which have been reported involve bidentate attack at the peri positions. The first reaction of this type used sodium disulphide as reagent[100] and led to the isolation of 2,3,4,5,6,7-hexachloronaphtho[1,8-cd]-1,2-dithiole. Klingsberg has extended this work to prepare this same compound, 2,3,6,7-tetrachloronaphtho[1,8-cd:4,5-c'd']bis[1,2]dithiole and 2,3,4,5,6,7-hexachloronaphtho[1,8-cd]-1,2-diselenole by reaction of octachloronaphthalene with sodium disulphide, elemental sulphur, and elemental selenium, respectively.[101]



B. Chlorinated Heterocyclic Aromatic Compounds

(i) Chloropyridines. Pentachloropyridine will undergo nucleophilic substitution with a wide range of nucleophiles in the 2- and 4-positions and the relative amounts of the two products, for a range of nucleophiles,

are shown in Table 1-1.[102]

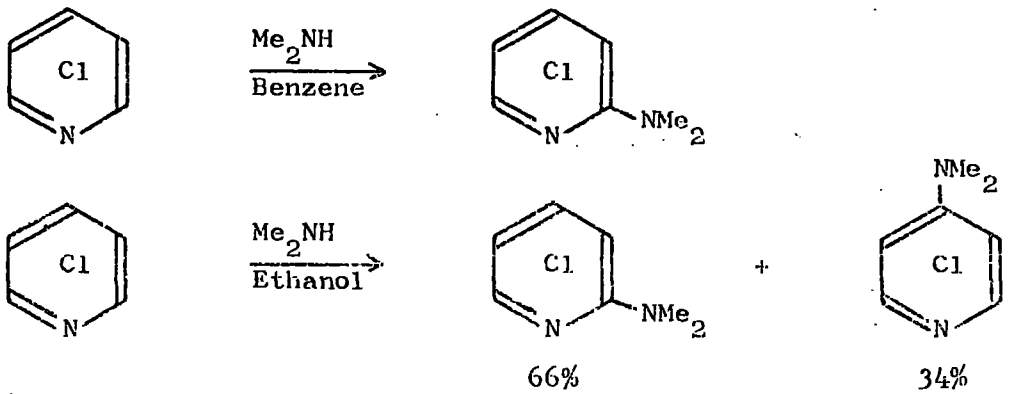
Table 1-1

Reactions of Pentachloropyridine with Various Nucleophiles

Nucleophile	Solvent	Ratio of 4:2
NH_3	EtOH	70:30
Me_2NH	EtOH	20:80
Et_2NH	EtOH	1:99
MeO^-	MeOH	85:15
EtO^-	EtOH	63:35
$nBuO^-$	nBuOH	57:43

As the nucleophile size increases, the relative amount of the 2-substituted compound also increases, indicating that steric effects are important but that, in their absence, 4-substitution is considerably more favoured than 2-substitution. Further substitution of these monosubstituted materials has been investigated[102] and 4-substituted pyridines react to give only 2,4-disubstituted pyridines. 2-Substituted pyridines, however, react to give both 2,4- and 2,6-disubstituted pyridines and the relative amount of 2,6-disubstitution increases with the size of the nucleophile.

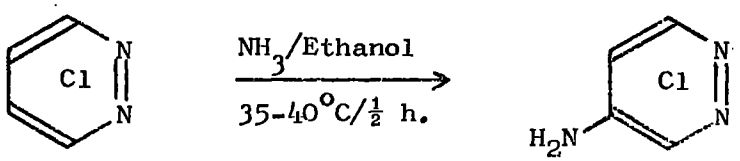
The nature of the solvent can also influence orientation for, in benzene as solvent, the reaction between pentachloropyridine and dimethylamine gives exclusively 2-substitution whereas, in ethanol as solvent, both 2- and 4-substitution occurs.[103]

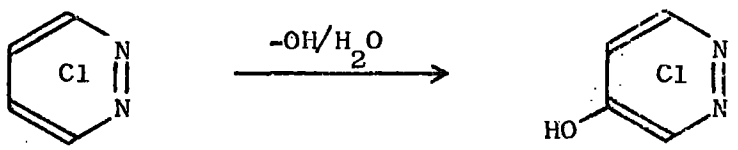


This type of solvent effect has been found to be quite general for any fairly bulky aliphatic amine.

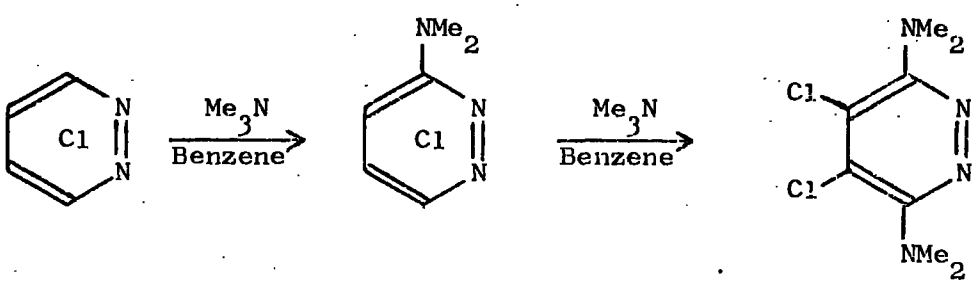
As with pentachlorobenzene derivatives, substitution in tetrachloropyridine derivatives can lead to the substituent being replaced. For example, both tetrachloro-2-nitropyridine and tetrachloro-4-nitropyridine react with a variety of nucleophiles to replace the nitro group, rather than a chlorine atom.[104]

(ii) Chlorodiazines. Tetrachloropyridazine reacts with ammonia or hydroxide ion to give substitution only in the 4-position.[105]



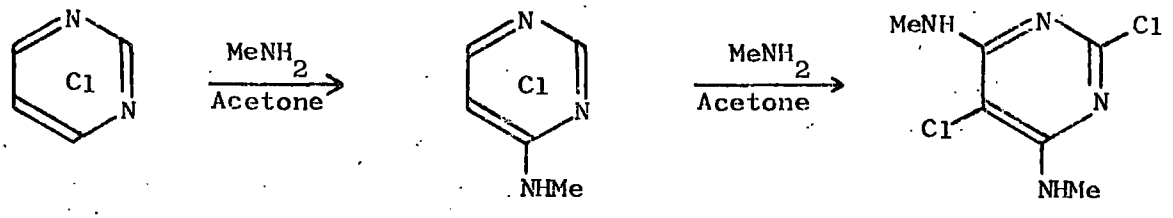


However, it seems that steric factors can be important because when a larger nucleophile, such as trimethylamine, is used, substitution occurs in the 3- and 6-positions to give quaternary ammonium salts which lose methyl chloride and produce 3-dimethylaminotrichloropyridazine and 3,6-bis-(dimethylamino)dichloropyridazine.[106]



Early work on the nucleophilic substitution of tetrachloropyrimidine by amines enabled a disubstituted product to be isolated, but its structure was not identified.[107] It has now been shown that it is possible to isolate a

monosubstituted compound and that substitution occurs in the 4- and 6-positions.[108]

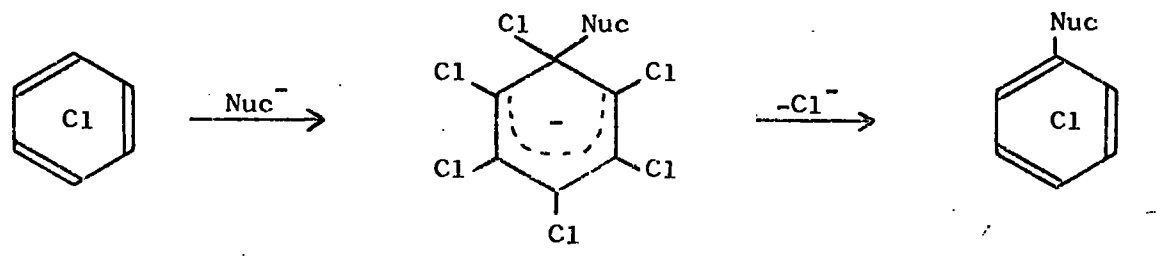


In the case of tetrachloropyrazine there is, of course, only one position in which monosubstitution can occur. Recent experiments suggest that, when disubstitution is achieved, small nucleophiles give 2,3-disubstituted pyrazines, whereas larger nucleohiles give 2,6-disubstituted pyrazines.[109]

C. Theoretical Aspects

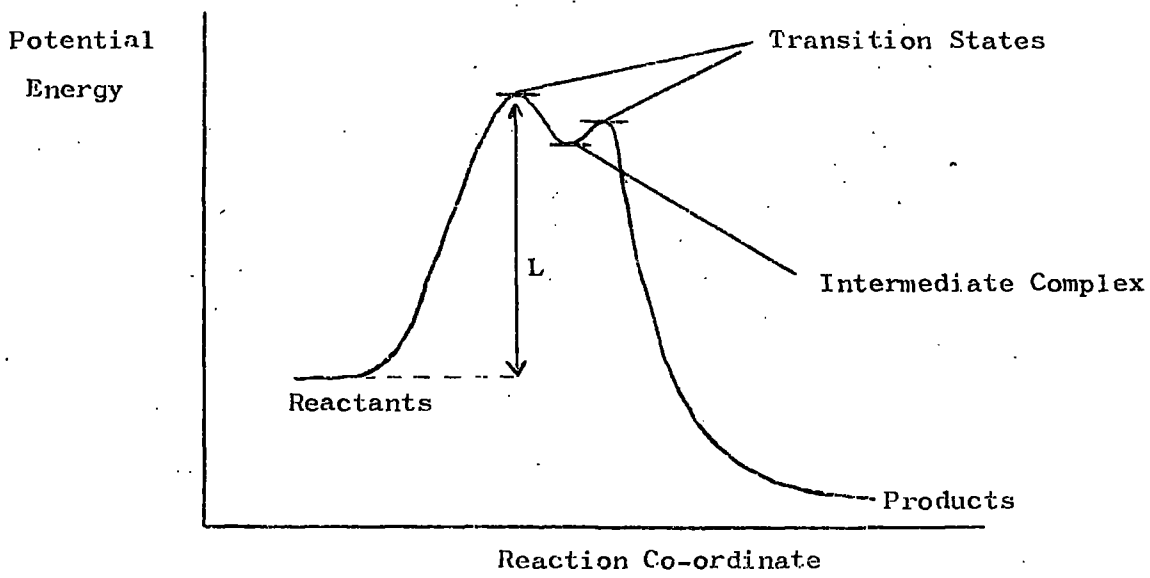
(i) General Points. Any theoretical investigation of the mechanism of nucleophilic substitution in chlorinated aromatic compounds should be able to rationalise two main facts. The first is why highly chlorinated compounds are generally much less reactive than the corresponding highly fluorinated compounds, and the second is why substitution occurs at particular ring positions.

It is clear that, if these observations are to be understood, the reaction mechanism must be known, and this is believed to involve a σ-bonded intermediate so that, for hexachlorobenzene, the mechanism may be represented as:

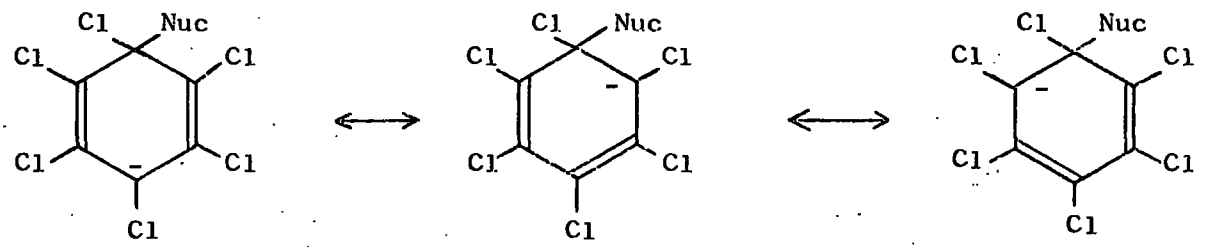


where Nuc^- is a general nucleophile. It is thought that the first step is

rate determining so that the energy profile of the reaction may be represented as below, passing through two transition states and the intermediate.



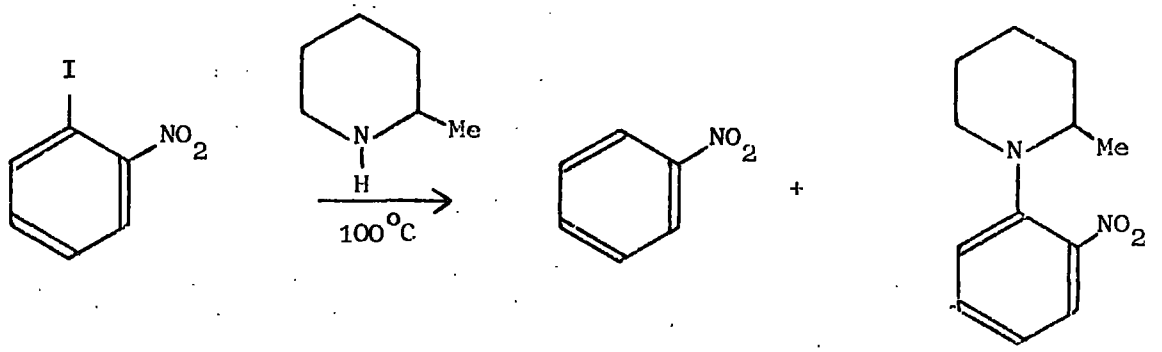
The height of the energy barrier, L, between the reactant and the first transition state, which is known as the localisation energy, will be critical in determining the ease of reaction, so it is important to understand the nature of the transition state. It is normally taken to be quite similar to the intermediate in which the simple valence bond descriptions indicate that charge is exclusively on the positions ortho and para to the point of substitution.



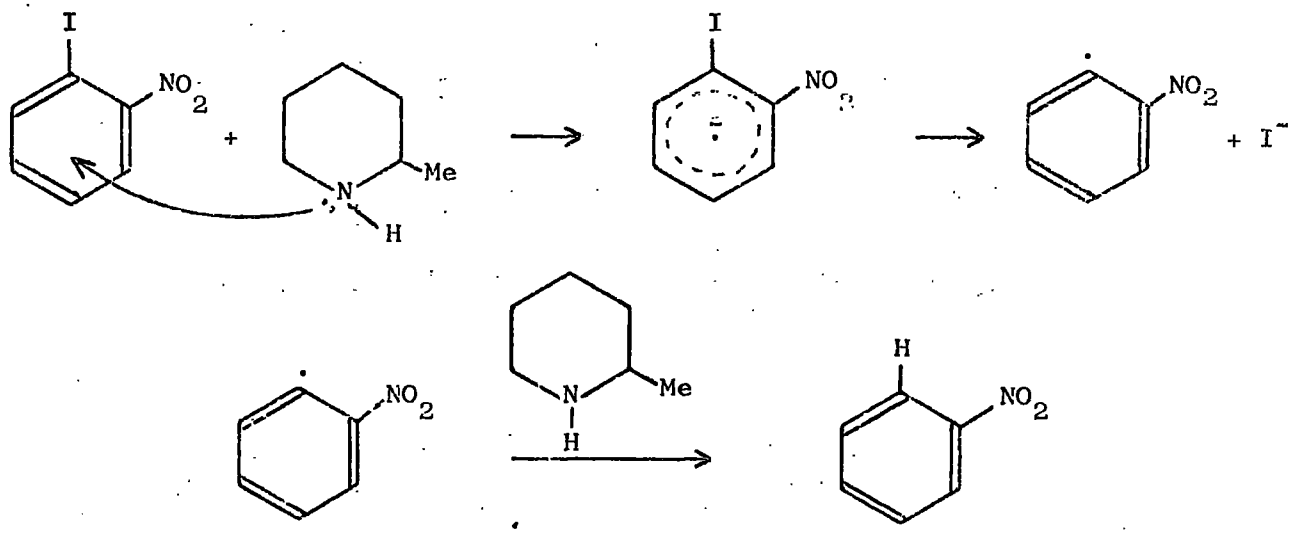
This charge distribution is confirmed by molecular orbital calculations.[110]

It must be remembered that this is not the only way that a nucleophile might react with an aromatic system, and the reaction of iodo-2-nitrobenzene with bulky amines, such as 2-methylpiperidine, which gives reductive de-

iodination, as well as substitution,[111] illustrates this.



In this case, it has been proposed[111] that the mechanism involves donation of an electron to the aromatic ring, giving a radical anion, loss of iodide ion, giving a phenyl radical, and hydrogen abstraction by this radical.

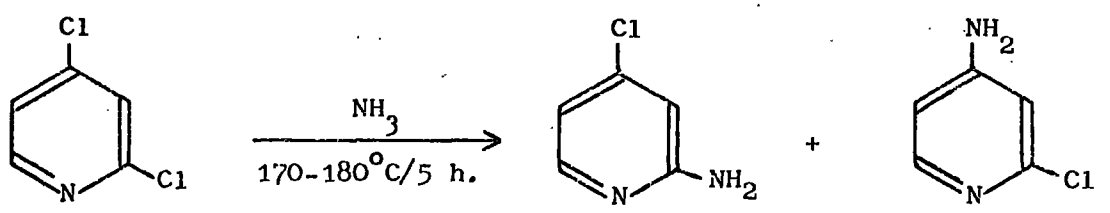


(ii) Reactivity of Chlorinated Compounds. The low reactivity of hexachlorobenzene, when compared to hexafluorobenzene, or of pentachloropyridine, when compared to pentafluoropyridine, might be thought to be caused by the greater electron withdrawing power of fluorine atoms reducing the energy of the negatively charged transition state, in the case of fluorine compounds. However, it is a general observation in aromatic systems that a carbon to fluorine bond is much more readily attacked by nucleophiles than a carbon to chlorine bond, and it seems likely that the greater susceptibility of fluorine to displacement is the cause of the greater reactivity of perfluorinated compounds.

It is commonly thought that fluoride ion is displaced more readily than chloride because the carbon to fluorine bond is more polar, and the carbon atom is therefore more positive and more open to nucleophilic attack.

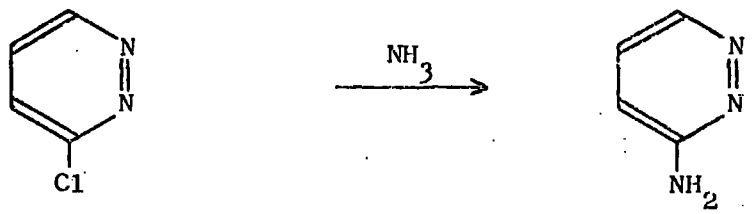
(iii) Effect of Ring Nitrogen. An important effect of ring nitrogen atoms is to activate the ring system to nucleophilic attack, so that pentachloropyridine is more reactive than hexachlorobenzene and pentafluoropyridine is more reactive than hexafluorobenzene. This activation is thought to arise from the electron accepting character of the nitrogen atom, which will reduce the energy of the transition state. It might also be thought that ring nitrogen atoms would influence the orientation of substitution, and the relative ease of displacement of halogen from the various monohalo heterocycles should provide information on such an influence.

In the case of pyridine, a wide range of nucleophilic substitution reactions of 2-chloropyridine and 4-chloropyridine has been reported, but no nucleophilic substitution reactions of 3-chloropyridine occur. Displacement from 2- and 4-positions, are illustrated by the conversion of 2,4-dichloropyridine to a mixture of 2-amino-4-chloropyridine and 4-amino-2-chloropyridine by reaction with ammonia.[112]



The effect of the ring nitrogen is therefore to activate the 2- and 4-positions of the pyridine ring to nucleophilic attack, but the degree of activation of the two positions is quite similar, for this reaction gives more substitution in the 4-position, whereas the Tschitschibabin reaction gives substitution at the 2-position exclusively.[113]

In the case of pyridazine, it has been shown that 3-chloropyridazines will undergo nucleophilic substitution readily, with a range of nucleophiles, whereas 4-chloropyridazine will not.[114] For example, 3-chloropyridazine is easily converted to 3-aminopyridazine by reaction with ammonia, whereas 4-chloropyridazine is much less reactive.



In the case of pyrimidine, the reaction of 2,4-dichloropyrimidine with methoxide ion, giving 2-chloro-4-methoxypyrimidine,[115] illustrates that the 4-position is activated to nucleophilic attack by the ring nitrogen atoms.

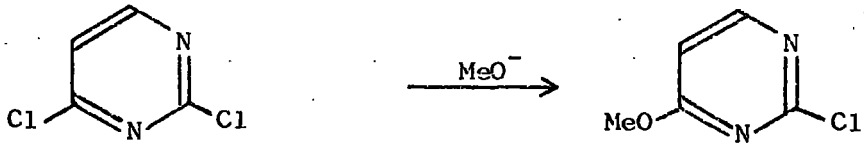
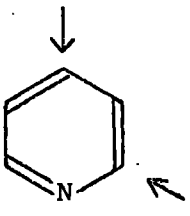
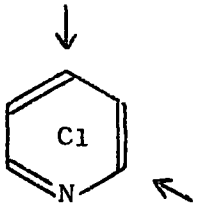
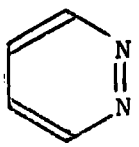
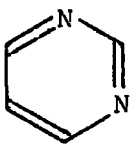


Table 1-2 compares the positions which reactions of the monohalo compounds show are activated to nucleophilic attack by the ring nitrogen, with the positions at which attack occurs in the perchlorinated nitrogen heterocycles. It is apparent that except for tetrachloropyridazine these positions are the same and that ring nitrogen is an important influence on the orientation of substitution, as is believed to be the case for perfluorinated nitrogen heterocycles, although the fluorine atoms also have an important effect.[29]

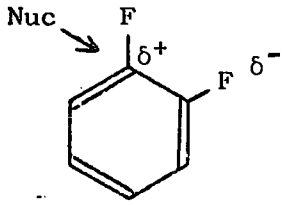
Table 1-2

Comparison of Substitution Positions in Monohalo- and Perchloro-heterocycles

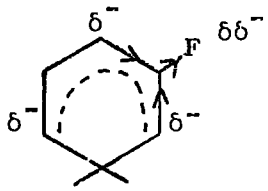
Position(s) Which Ring Nitrogen Activates	Position(s) Where Attack Occurs in Perchlorinated Compounds
	
	
	

(iv) Effect of Substituents. The orienting influence arising from the ring nitrogen leaves some experimental observations unexplained, notably the preference of pentachlorobenzene to undergo nucleophilic attack in the position para to the hydrogen atom, the considerably greater reactivity of the 4-position, compared to the 2-position in pentachloropyridine, in the absence of steric effects, and the preferred reaction of tetrachloropyridazine in the 4-position. This orientation is similar to that which has been observed for pentafluorobenzene and pentafluoropyridine, where it has recently been proposed that nucleophilic substitution occurs so as to maximise the number of fluorine atoms ortho and meta to the position of substitution.[116,117] Rate measurements on fluorohydropyridines show that a fluorine atom para to the position of substitution is slightly destabilising relative to hydrogen by a factor of 3,[118] when ortho to the position of substitution fluorine is

activating by a factor of 30,[118] and when meta to the position of substitution fluorine is activating by a factor of 23.[119] The small effect of a fluorine atom in the para position is thought to be because, in the transition state, destabilising electron pair repulsions are approximately balanced by electron withdrawal.[120] The activating influence of an ortho fluorine cannot be caused by stabilisation of the transition state but, rather, is believed to arise from a polarisation of the ground state, increasing the positive charge at the site of substitution as shown.[120]



The activating influence of a meta fluorine is thought to be due to the stabilisation of the transition state by electron withdrawal as shown.[120]



There has been very little comment on the orientation of nucleophilic substitution in chlorinated compounds in the literature, but the influence of chlorine, compared to fluorine in chlorofluoropyridines has been measured.[121] These results show that a chlorine atom ortho to the position of substitution is more activating than fluorine by a factor of about 3, meta chlorine and fluorine are approximately equivalent, and that para chlorine is more activating than fluorine by a factor of about 26. These results are summarised in Table 1-3, which gives ratios of rate constants. This table also shows the predicted influence of chlorine relative to hydrogen in the three positions, calculated by combining the other ratios, but it would be desirable to have these ratios measured directly in

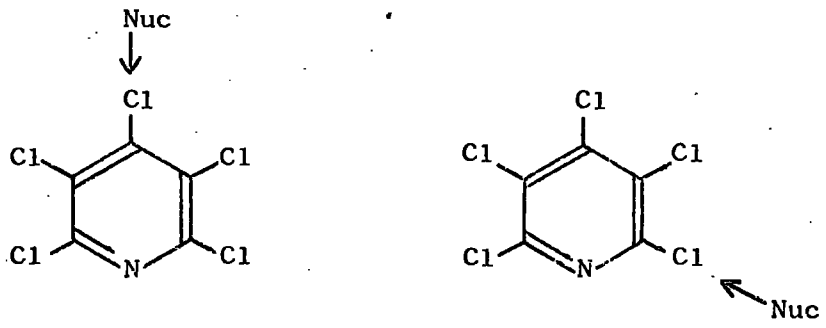
chlorohydropyridines, since the multiplication of the other ratios together will also have multiplied the errors.

Table 1-3

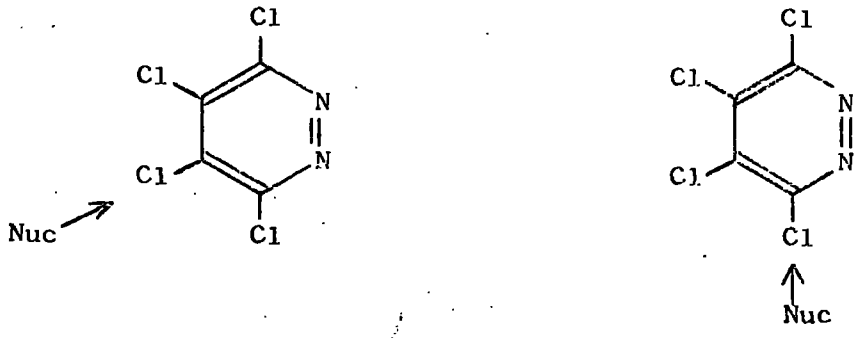
Ratios of Rate Constants for Reactions of Pyridines Substituted in Various Positions

Position	k_F/k_H	k_{Cl}/k_F	k_{Cl}/k_H
Ortho	30	3	90
Meta	23	1	34
Para	1/3	26	9

Using these values it appears that, as with fluorine compounds, nucleophilic substitution will occur in chlorine compounds at the position which maximises the number of chlorine atoms ortho or meta, but especially ortho, to the position of substitution. This is in accord with the observed orientation in pentachloropyridine and pentachlorobenzene, since, in pentachloropyridine, when nucleophilic attack occurs in the 4-position there are two ortho and two chlorine atoms, whereas when attack occurs in



the 2-position there are an ortho, two meta and one para chlorine atoms. This approach can also rationalise the orientation of substitution in tetrachloropyridazine which occurs preferentially in the 4-position, provided the nucleophile is not very large.



When attack occurs in the 4-position there are two ortho and one meta chlorine atoms, whereas when attack occurs in the 3-position there are one ortho, one meta and one para chlorine atoms. The magnitude of this influence, in this case, is presumably sufficient to overcome the influence of the ring nitrogen atom which makes the 3-position more susceptible to attack, although probably not by a very large amount.

Substituents other than chlorine can alter the orientation in a way which will depend upon whether they are electron withdrawing or electron donating.

3.3 Basicities

There have been very few measurements reported on the basicities of perchlorinated heterocyclic nitrogen compounds. However, the base strengths of various chlorinated pyridines have been quantitatively measured by a spectroscopic method, using sulphuric acid as the protonating agent.[122] The observed pKa values are given in Table 1-4.

Table 1-4

Basicities of Chlorinated Pyridines

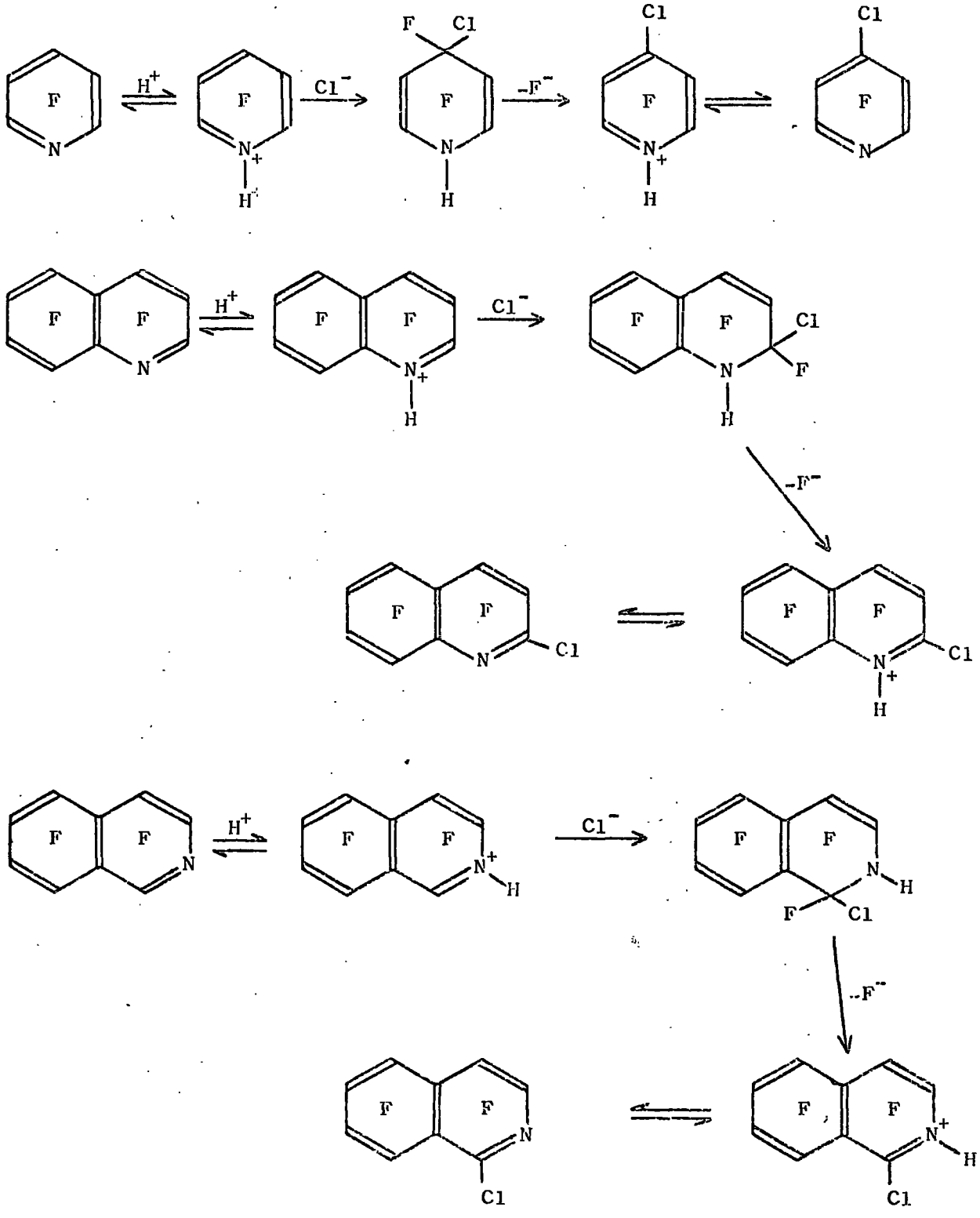
Compound	pKa
3,5-Dichloropyridine	0·75 ± 0·03
2,3-Dichloropyridine	-0·85 ± 0·01
2,6-Dichloropyridine	-2·86 ± 0·02
2,3,5,6-Tetrachloropyridine	-5·50 ± 0·02
Pentachloropyridine	-6·02 ± 0·02

When compared with the value for pyridine itself,[123] which is +5·2, it is apparent that substitution of chlorine into a heterocyclic nitrogen system reduces the base strength considerably, but to an extent which depends upon the position of substitution. For example, chlorine atoms substituted in the positions ortho to the nitrogen atom of pyridine reduce the base strength more than chlorine atoms substituted in the meta positions. It is not difficult to postulate a reason for this observed reduction in base strength. The electron withdrawing nature of the substituted chlorine atoms will reduce the lone pair electron density on the nitrogen atom, and so reduce the base strength of the molecule. This effect will be greatest when the substituent is in the positions ortho to the nitrogen atom.

Since fluorine is more electron withdrawing than chlorine, it might be expected that pentafluoropyridine would be even less basic than pentachloropyridine and crude measurements confirm this prediction, giving a pKa value of about -11.[124,125] This is a very low value and early experiments on pentafluoropyridine indicated that it was effectively non-basic.[1,95,126,127] More recently it has been possible to isolate hexafluoroantimonate salts of a variety of perfluorinated heterocyclic nitrogen compounds, including pentafluoropyridine, and the order of basicity of the perfluorinated nitrogen heterocycles has been deduced by n.m.r. measurements.[124,128] These show that the basicity is largely determined by the number of fluorine atoms ortho to the nitrogen atom - the fewer ortho fluorine atoms there are, the greater is the basicity. Thus tetrafluoropyridazine is more basic than tetrafluoropyrimidine and heptafluoroquinoline is more basic than heptafluoroisoquinoline. This type of effect would also be expected in the perchlorinated nitrogen heterocycles.

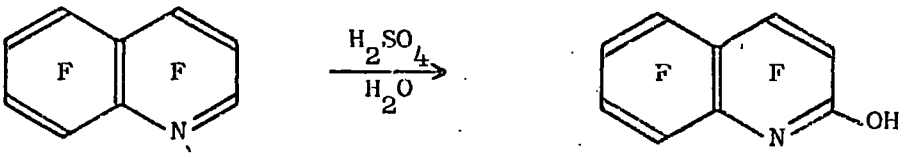
The base strength has been found to parallel the reactivity in certain reactions. For example, pentafluoropyridine, heptafluoroquinoline and

heptafluoroisoquinoline have been found to react with gaseous hydrogen chloride in sulpholane solution, to replace fluorine by chlorine.[129] This is believed to occur via protonation.



The order of reactivity is heptafluoroquinoline >>> heptafluoroisoquinoline > pentafluoropyridine, which parallels the order of base strength.

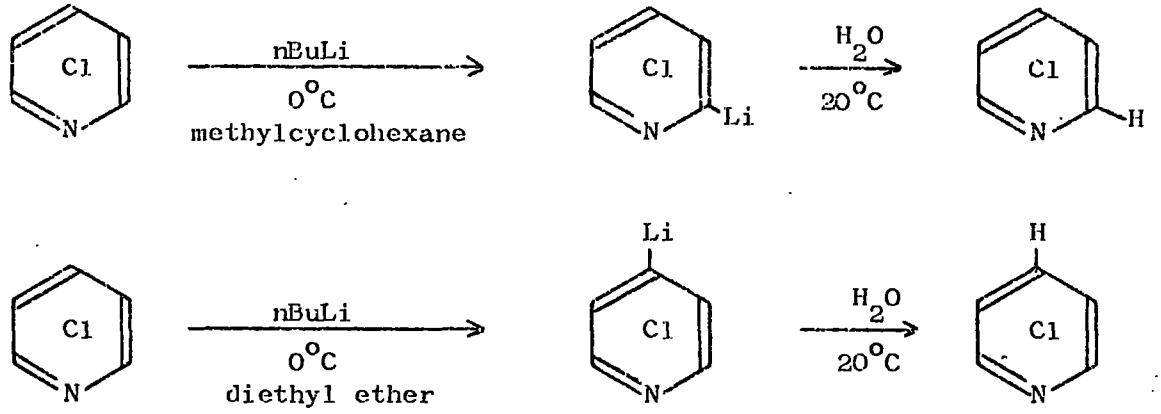
The base strength also parallels the ease of acid hydrolysis, for heptafluoroquinoline is hydrolysed by aqueous sulphuric acid to hexafluoro-2-hydroxyquinoline, whereas heptafluoroisoquinoline and pentafluoropyridine are unaffected.[130]



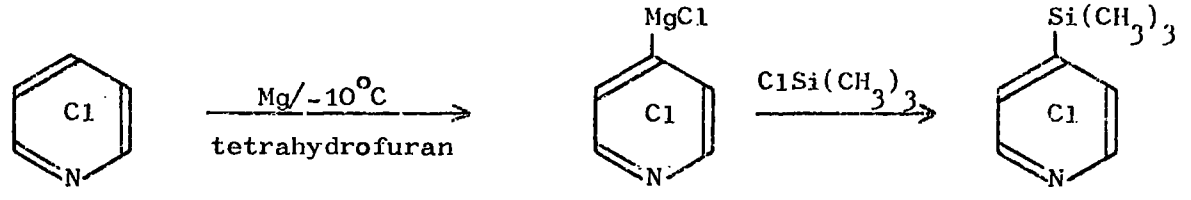
By analogy, perchloroheterocyclic compounds would be expected to be more basic, and therefore more susceptible to acid induced reactions such as hydrolysis, as the number of chlorine atoms ortho to the nitrogen is reduced. However, the observation that heptachloroquinoline, which is presumably more basic than heptafluoroquinoline, is unaffected by aqueous sulphuric acid,[130] throws considerable doubt upon this prediction, although this observation was made from experiments at room temperature only.

3.4 Reactions with Organometallic Compounds

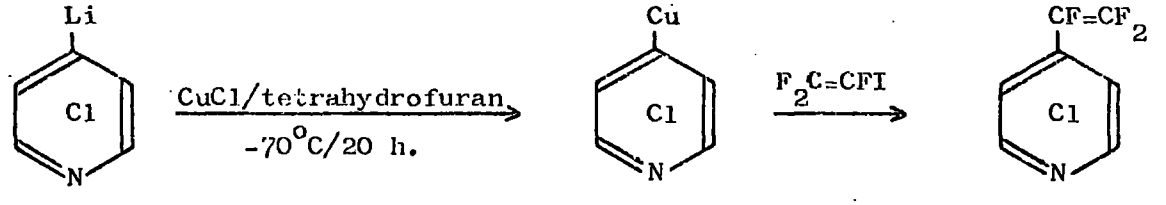
There has been a considerable amount of work carried out investigating the reactions of highly chlorinated pyridines with organometallic reagents. Most commonly, the reagent used is an alkyl lithium. The reaction normally occurs to give metal exchange with the production of a pyridyl lithium, and the pyridyl lithium is normally identified by hydrolysing to the hydro compound. The nature of the solvent has a profound effect on the reaction. For example, when pentachloropyridine is reacted with n-butyl lithium in hydrocarbon solvents, such as methylcyclohexane, and then hydrolysed, 3,4,5,6-tetrachloropyridine is isolated; when pentachloropyridine is reacted with n-butyl lithium in diethyl ether, and then hydrolysed, 2,3,5,6-tetrachloropyridine is obtained.[131,132]



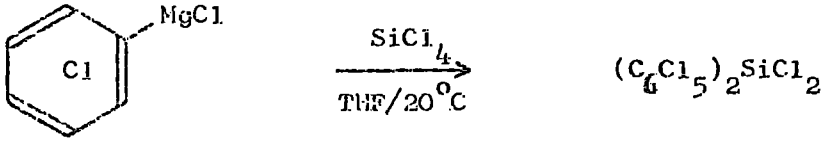
Mercury and magnesium derivatives have also been obtained.[132,133] For example, pentachloropyridine reacts with magnesium to give tetrachloro-4-pyridyl magnesium chloride, as shown by reacting this with chlorotrimethylsilane.[133]



Copper derivatives of pentachloropyridine have also been reported.[134] They have been prepared by reacting tetrachloro-4-pyridyl lithium with cuprous chloride and they will react with trifluoroiodoethylene to displace iodine.



In the hydrocarbon series, a whole range of silicon and tin derivatives has been prepared by reaction of pentachlorophenylmagnesium chloride with silanes and stannanes.[135,136]



$$C_6Cl_5MgCl \xrightarrow[THF/20^{\circ}C]{SiF_4} (C_6Cl_5)_3SiF$$

$$C_6Cl_5MgCl \xrightarrow[THF/20^{\circ}C]{Ph_3SiCl} C_6Cl_5SiPh_3$$

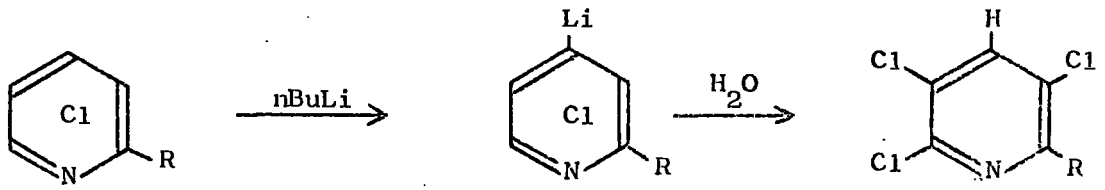
$$C_6Cl_5MgCl \xrightarrow[THF/20^{\circ}C]{Ph_2SiCl_2} (C_6Cl_5)_2SiPh_2$$

$$C_6Cl_5MgCl \xrightarrow[THF/20^{\circ}C]{Ph_3SnCl} C_6Cl_5SnPh_3$$

$$C_6Cl_5MgCl \xrightarrow[THF/20^{\circ}C]{Ph_2SnCl_2} (C_6Cl_5)_2SnPh_2$$

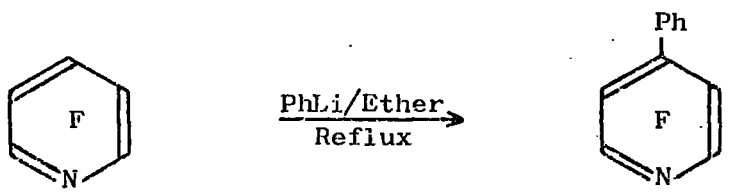
$$C_6Cl_5MgCl \xrightarrow[THF/20^{\circ}C]{SnCl_4} (C_6Cl_5)_4Sn$$

Tetrachloro-2-pyridyl derivatives generally react with n-butyl lithium in the same way to give metallation at the 4-position.[137]

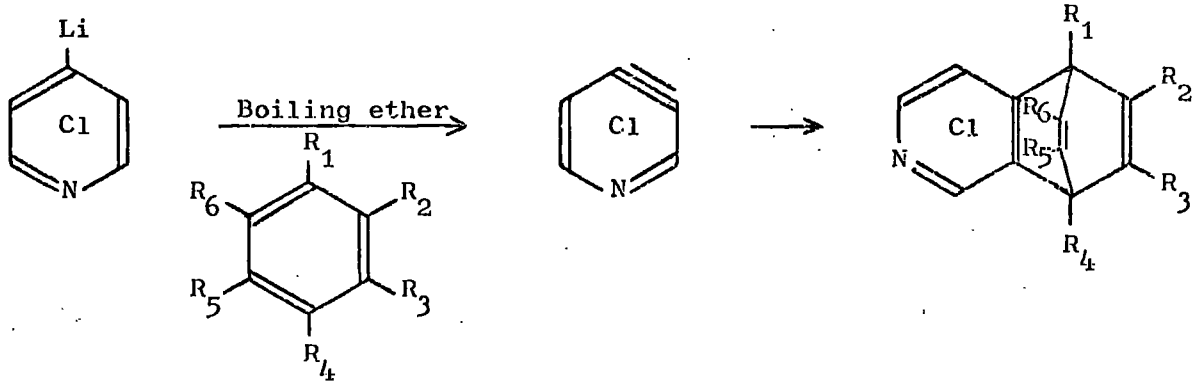


This reaction has been shown to occur where R is methoxy, dimethylamino, piperidino or pyrrolidino.

This metallation reaction which occurs with pentachloropyridine is in marked contrast to the reaction between alkyl lithiums and perfluorinated nitrogen heterocycles, where alkylation occurs. For example, pentafluoropyridine reacts with phenyl lithium to give tetrafluoro-4-phenylpyridine.[126]

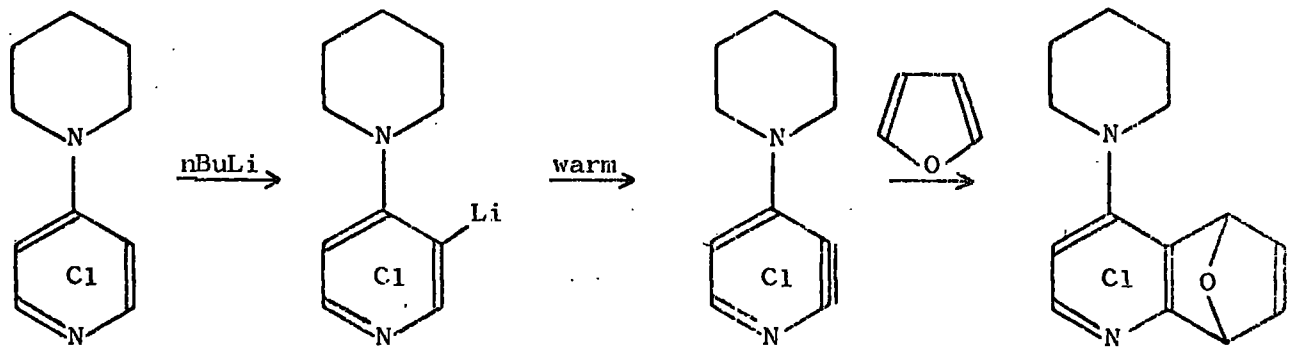


The chlorinated pyridyl lithiums are reasonably stable, even at room temperature, but there is evidence that they can lose lithium chloride to form transient pyridyne species. Trichloro-3-pyridynes seem to be much more readily formed than trichloro-2-pyridynes.[138,139] For example, if tetrachloro-4-pyridyl lithium is boiled in ether in the presence of any methyl substituted benzene, 1,4-addition products are obtained.

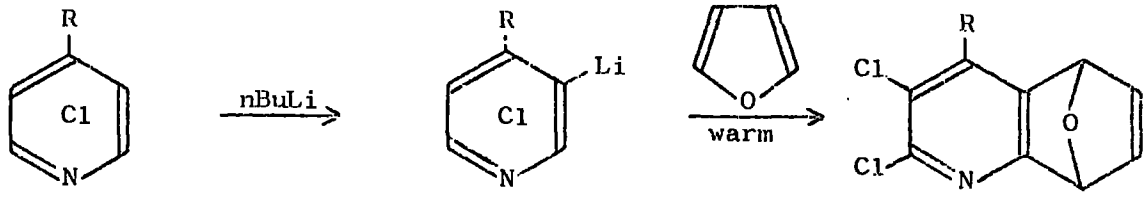


All the R groups may be either methyl or hydrogen. A corresponding reaction for tetrachloro-2-pyridyl lithium only occurs with mesitylene, and in low yield.

It has been possible to isolate furan adducts of 2-pyridynes which derive from 3-pyridyl lithiums. Tetrachloro-4-piperidinopyridine reacts with n-butyl lithium to give the 3-pyridyl lithium which, on warming in the present of furan forms an adduct of trichloro-4-piperidino-2-pyridyne.[140]

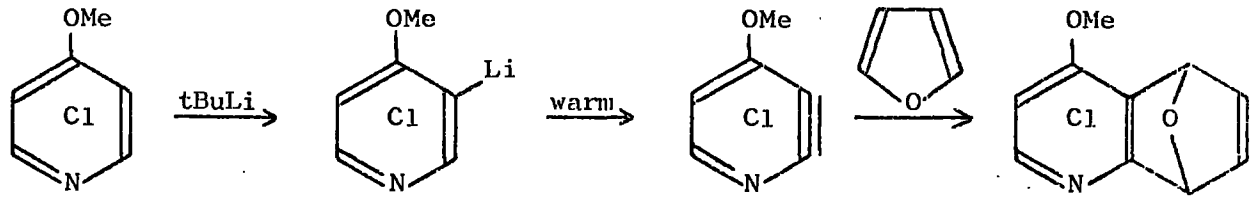


It has been shown that this reaction occurs for a range of 4-substituted tetrachloropyridines.[141]

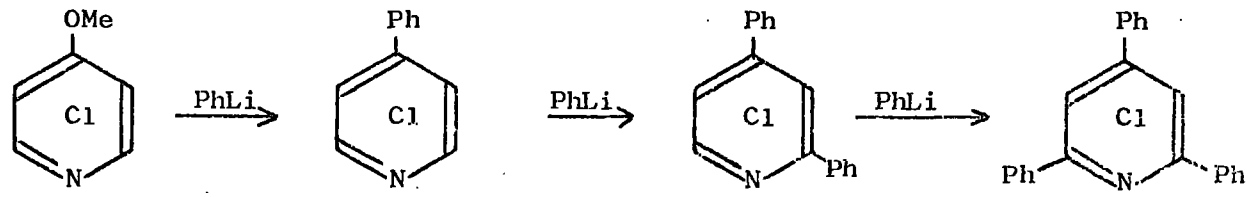


The R group may be dimethylamino or pyrrolidino, as well as piperidino.

Tetrachloro-4-methoxypyridine reacts with alkyl lithiums in a manner which depends on the alkyl group. With t-butyl lithium the reaction proceeds as above, via the 3-pyridyl lithium and the 2-pyridyne.[142]

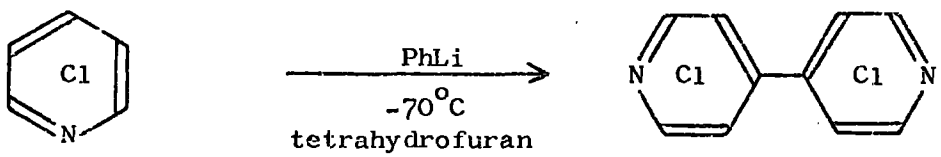


However, with phenyl lithium, alkylation occurs, first in the 4-position and then in the positions ortho to the nitrogen atom.[143]



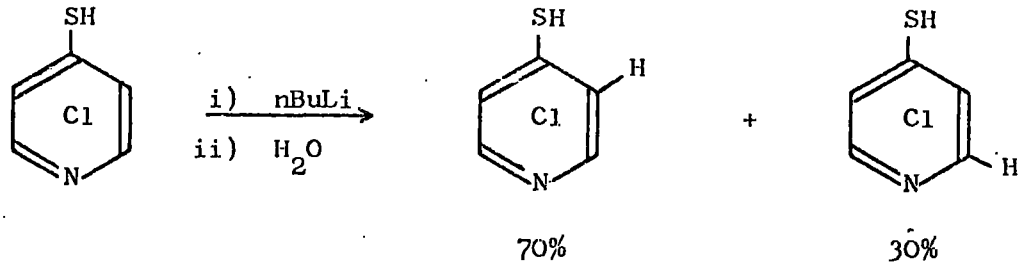
A corresponding reaction occurs with 4-methoxyphenyl lithium, 4-dimethylaminophenyl lithium, and 4-trifluoromethylphenyl lithium.[143]

Phenyl lithium has been found to react with pentachloropyridine to give octachloro-4,4'-bipyridine, presumably by reaction of tetrachloro-4-pyridyl lithium with unreacted pentachloropyridine.[144]

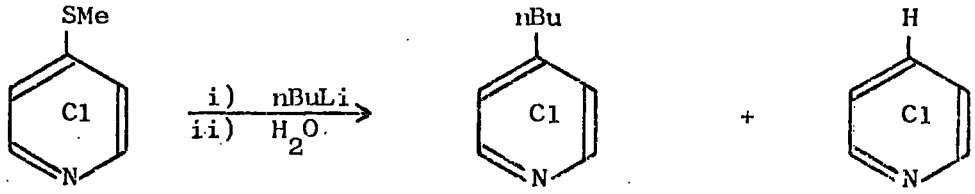


Tetrachloro-4-pyridyl derivatives, where the substituted group contains sulphur, have also been reacted with n-butyl lithium.[145,146] Tetrachloro-

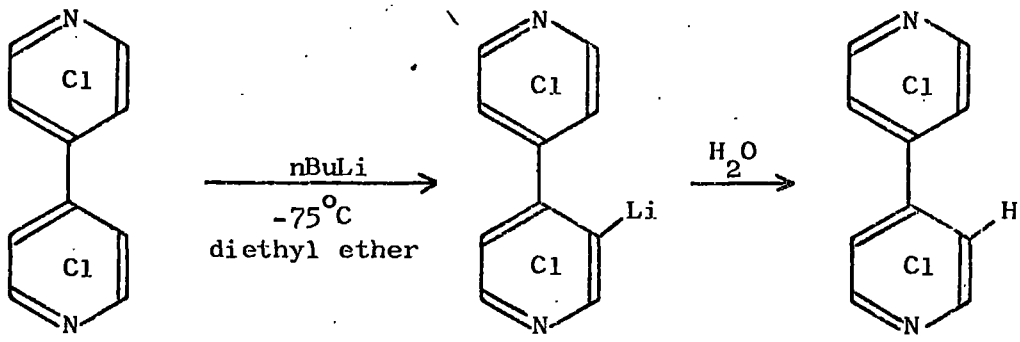
4-mercaptopyridine reacts to give metallation at the 2- and 3-positions, as shown by the products of hydrolysis.



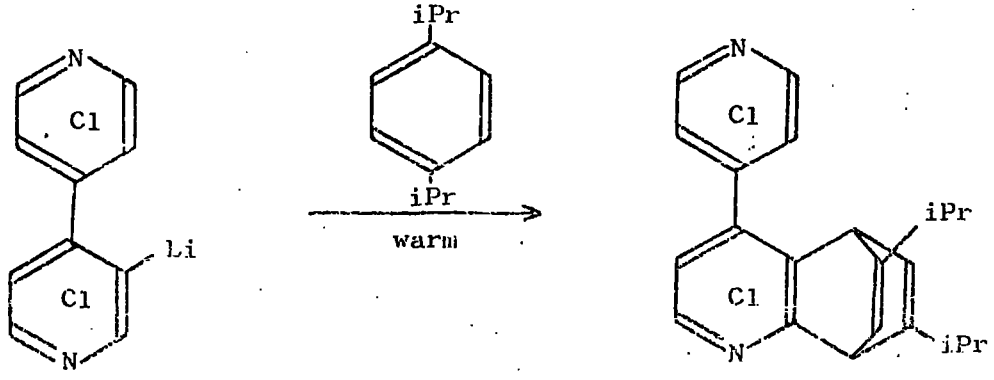
The methylated thioether, however gives largely substitution, or even metallation, at the 4-position so that 4-n-butyltetrachloropyridine and 2,3,5,6-tetrachloropyridine are produced.



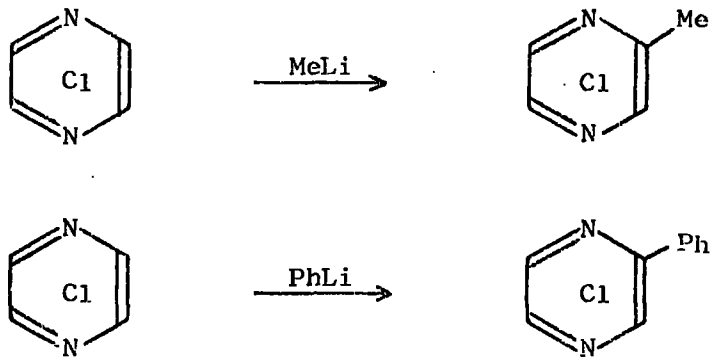
A heptachlorobipyridyl lithium has also been prepared by reaction of 4,4'-octachlorobipyridyl with n-butyl lithium in diethyl ether.[147] The identity of this organometallic reagent is revealed by hydrolysing it.



If the lithium compound is warmed in the presence of 1,4-bis-isopropylbenzene, an adduct of the aryne is produced.



There has been virtually no work done on the reactions of other chlorinated heteroaromatic systems of nitrogen with organometallic reagents. It has been found that tetrachloropyrazine tends not to react like pentachloropyridine to give metallation, but rather to give alkylation.[68] Thus methyl lithium and phenyl lithium react to give trichloromethylpyrazine and trichlorophenylpyrazine, respectively.

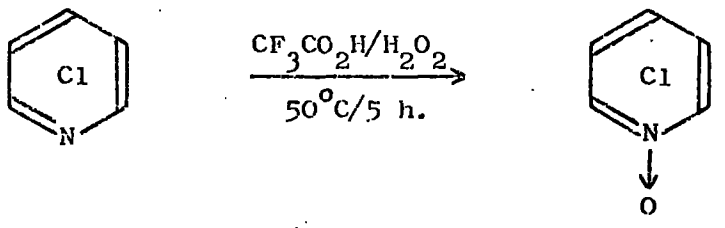


When tetrachloropyrazine is treated with n-butyl lithium, however, no recognizable products are obtained.

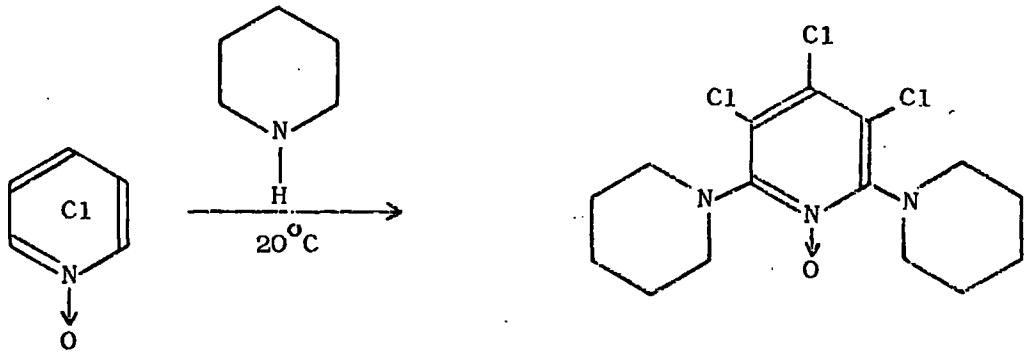
In general, it seems that the reactions of perchlorinated heteroaromatic compounds containing nitrogen with organometallic reagents are rather complicated and not properly understood.

3.5 Perchlorinated N-Oxides

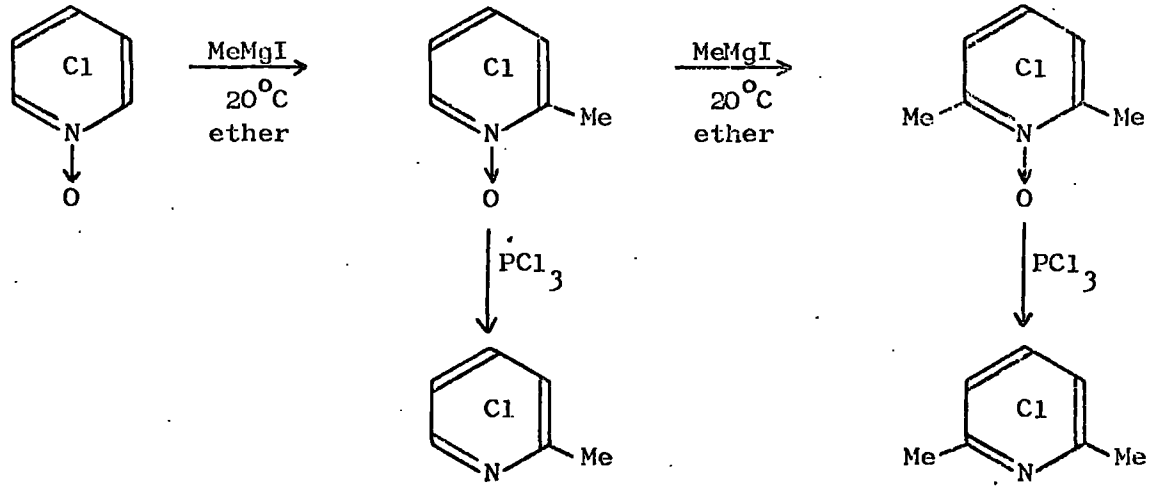
It is difficult to oxidise a nitrogen atom in a perchlorinated heterocyclic compound to give the N-oxide, presumably because of its low basicity. Following the observation that trifluoroperacetic acid oxidises 2,6-dichloropyridine in good yield,[148] this reagent has been used to oxidise pentachloropyridine, in yields of only about 20%.[104,149]



Not surprisingly, pentachloropyridine-1-oxide has been found to be more susceptible to nucleophilic attack than pentachloropyridine itself and attack occurs only in the 2- and 6-positions.[104] For example, it reacts with piperidine to give trichloro-2,6-dipiperidinopyridine-1-oxide

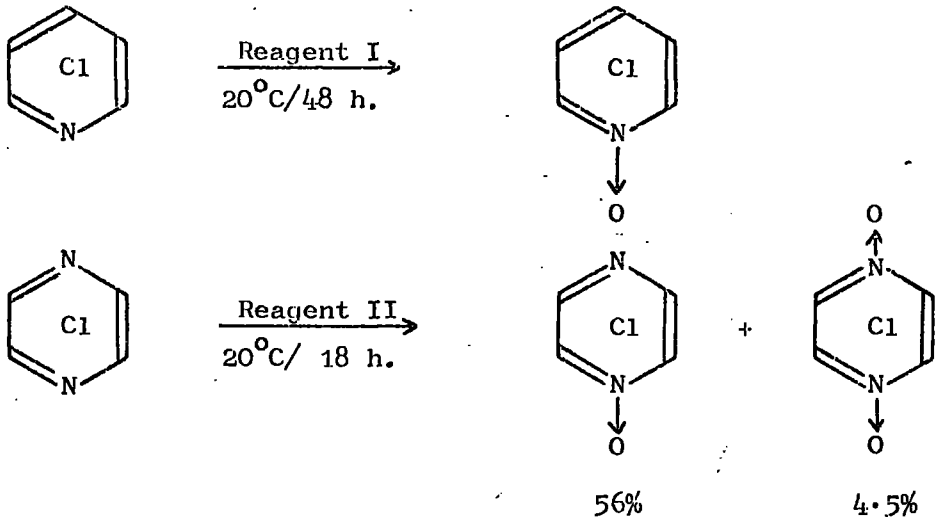


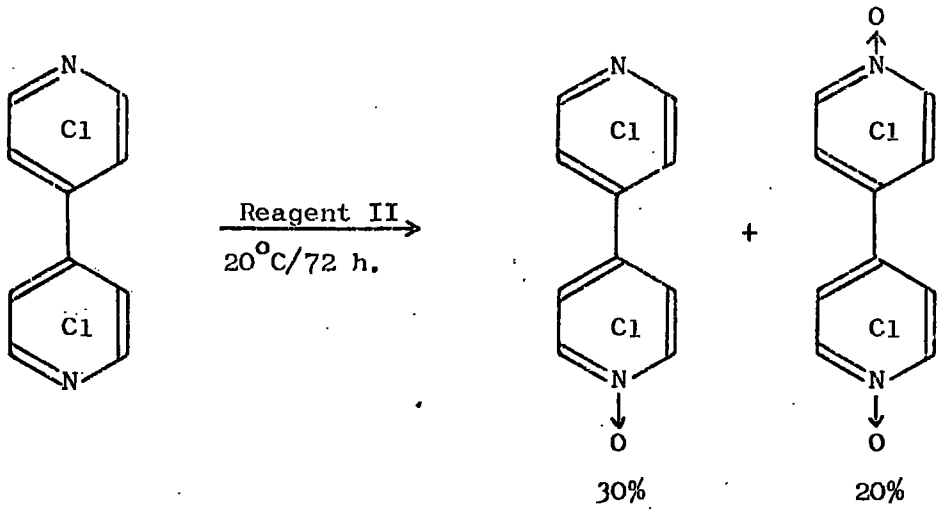
Also, pentachloropyridine-1-oxide will react with Grignard reagents, in contrast to pentachloropyridine itself. Since the N-oxides can be deoxygenated with phosphoryl chloride, this provides a convenient route to tetrachloro-2-methylpyridine and trichloro-2,6-dimethylpyridine.[150]



As noted earlier, trifluoroperacetic acid only converts pentachloropyridine to its N-oxide in yields of about 20%. Chivers and Suschitzky have developed two new reagents for oxidising perchloroheteroaromatic compounds on the heterocyclic nitrogen atom.[151,152] The first reagent is a mixture of acetic acid, concentrated sulphuric acid and 90% hydrogen peroxide; the second reagent is a mixture of trifluoroacetic acid,

concentrated sulphuric acid and 90% hydrogen peroxide. These reagents have been used to prepare pentachloropyridine-1-oxide in 85% yield, as well as N-oxides of tetrachloropyrazine and octachloro-4,4'-bipyridine.



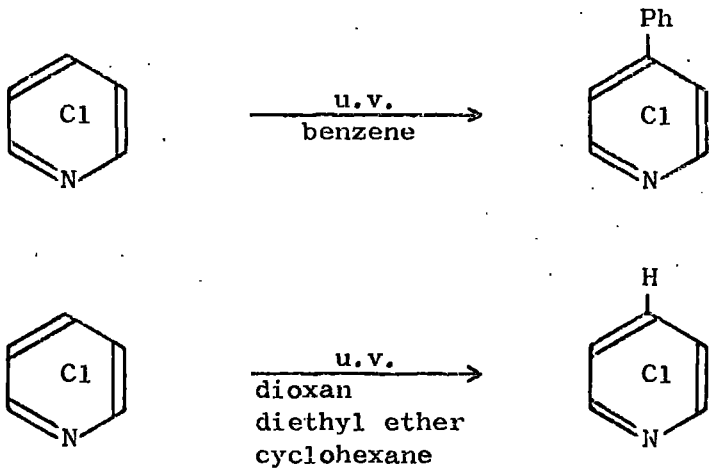


These reagents are not universally applicable, however. Tetrachloropyridazine, heptachloroquinoline, heptachloroisoquinoline and hexachlorocinnoline give no reaction unless the mixture is heated, and then hydrolysis occurs. There is some evidence that tetrachloropyrimidine may be converted to the 1-oxide, but the results were not reproducible.

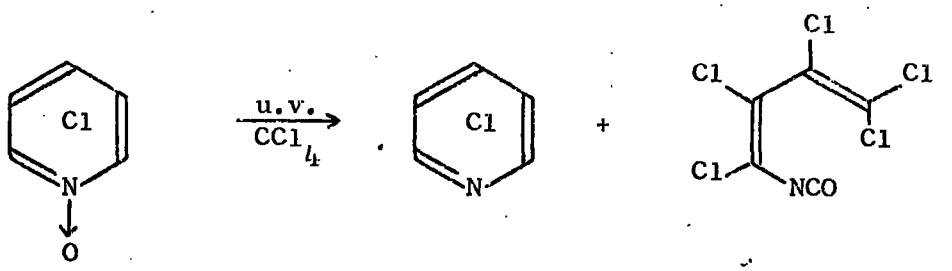
3.6 Pyrolysis and Photolysis Reactions

The photolysis of perchlorinated aromatic systems has not been much investigated and the most common reaction seems to involve breakage of the

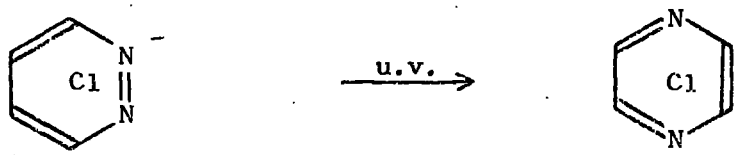
carbon to chlorine bonds homolytically. Photolysis of pentachloropyridine with a medium pressure mercury lamp, in benzene solution produces tetrachloro-4-phenylpyridine, and in a range of other solvents the major product is 2,3,5,6-tetrachloropyridine.[153]



The photolysis of pentachloropyridine-1-oxide in carbon tetrachloride gives a completely different reaction,[153] because, as well as producing pentachloropyridine, ring opening occurs to give pentachlorobutadienyl-1-isocyanate and there is considerable degradation.

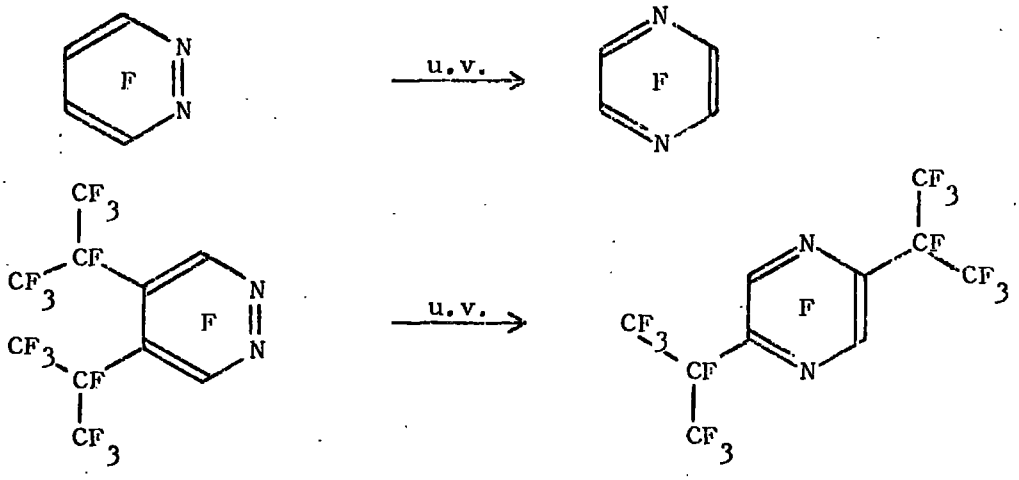


There has been one report of a rearrangement reaction occurring by the photolysis of a perchloroheteroaromatic system,[154] and this was the conversion of tetrachloropyridazine to tetrachloropyrazine by photolysis in inert solvents.



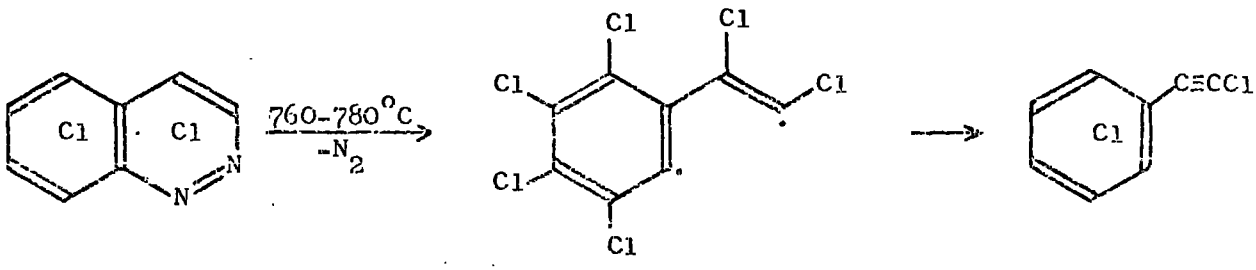
Attempts to repeat this reaction under a variety of conditions, however, have given very poor yields of tetrachloropyrazine and extensive decomposition.[155]

Despite this, the last rearrangement reaction suggests that perchloro-heterocyclic compounds may be as versatile as perfluoroheterocyclic compounds in undergoing a wide range of photochemically initiated rearrangements. Typical of these are the isomerisation of tetrafluoro-pyridazine to tetrafluoropyrazine and of difluoro-4,5-bis(heptafluoro-isopropyl)pyridazine to difluoro-2,5-bis(heptafluoroisopropyl)pyrazine, under the influence of light from a medium pressure mercury lamp.[156]

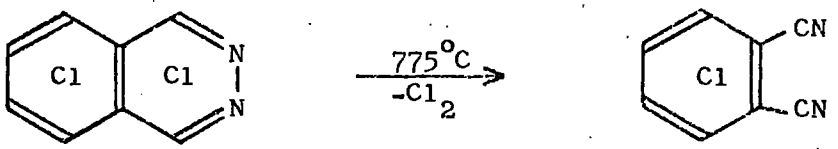


The mechanism of these rearrangements is unclear, but diaza dewar benzenes have been isolated.[157]

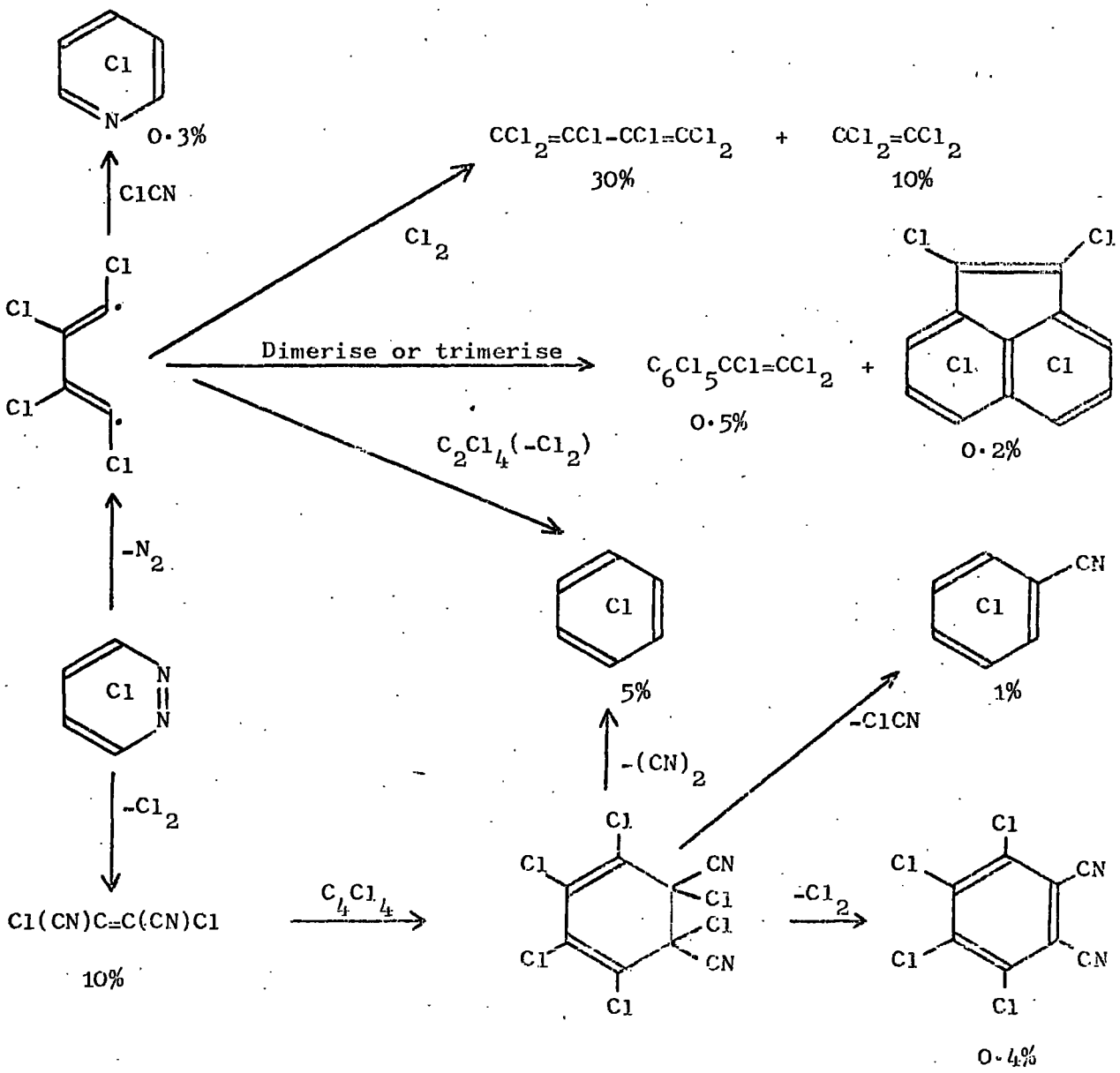
Pyrolyses which have been most studied are those where two nitrogens are next to one another in a chlorinated heterocyclic ring. Generally, reaction can proceed in two ways. First, loss of nitrogen can occur, and this is what happens with hexachlorocinnoline where the resulting di-radical undergoes a rearrangement to give hexachlorophenylacetylene in 37% yield.[158]



Secondly, the nitrogen to nitrogen bond may break with loss of chlorine, so that a dinitrile is produced. This is what is observed with hexachlorophthalazine, tetrachloro-1,2-dicyanobenzene being formed in 92% yield.[158]



The pyrolysis of tetrachloropyridazine itself is more complex because both of these two processes occur and the major products are hexachlorobutadiene, tetrachloroethylene, hexachlorobenzene and both isomers of 1,2-dichlorodicyanoethylene.[158] The transformations which it is proposed occur in this reaction, are as shown below.



DISCUSSION

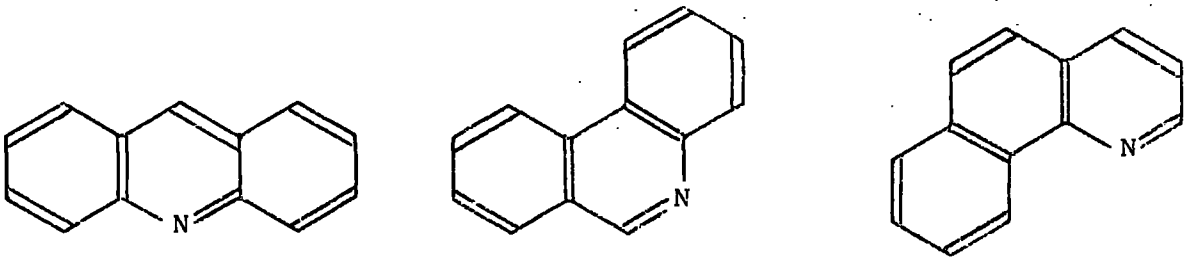
CHAPTER II

Syntheses of Some Perchloroheterocyclic Compounds Containing Nitrogen

1. Introduction

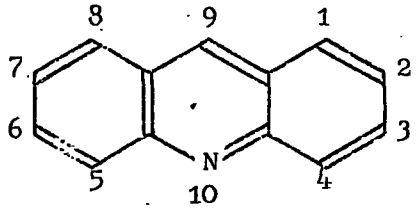
1.1 Ring Systems, Numbering and Nomenclature

Three tricyclic ring systems containing one nitrogen atom were investigated and they were the systems shown below:

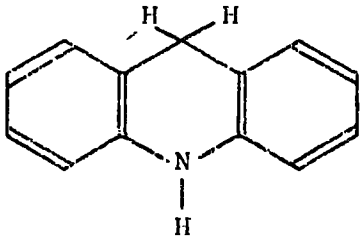


These compounds are normally known as acridine, phenanthridine and 7,8-benzoquinoline, respectively.

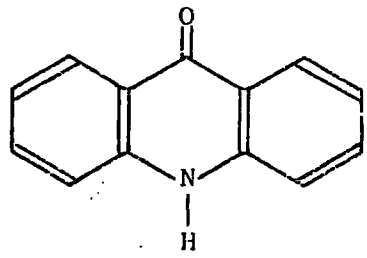
Today acridine is always numbered as shown below, with the nitrogen atom in the 10-position, and most publications on acridines use this numbering system:



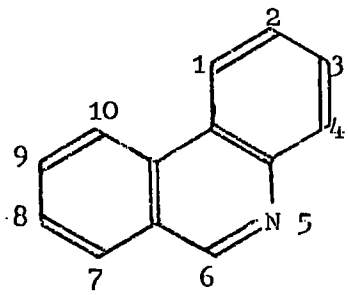
Like anthracene, the 9,10 positions are particulary reactive, and acridine may be partially reduced across the 9- and 10-positions to give a dihydroacridine, which is known as acridan.



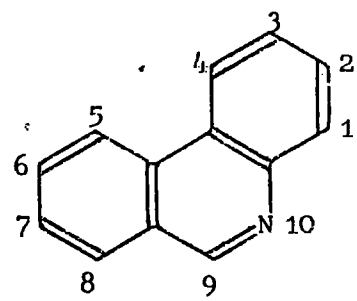
Acridine may also be oxidised to a ketone, commonly known as acridone but more properly called 9-acridanone.



The correct numbering system for phenanthridine places the nitrogen atom in the 5-position, as shown:

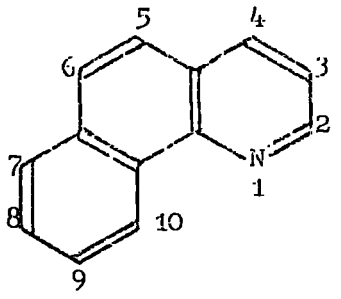


However, an earlier numbering scheme in which the nitrogen atom is in the 10-position, is frequently used in the literature, as shown below, and care must be taken to avoid confusion.



Like acridine, phenanthridine may be reduced or oxidised to give the corresponding phenanthridan and 6-phenanthridanone.

7,8-Benzoquinoline is named as a quinoline because in its properties it closely resembles quinoline. However, it is much better to describe it as 1-azaphenanthrene and use the numbering system shown:

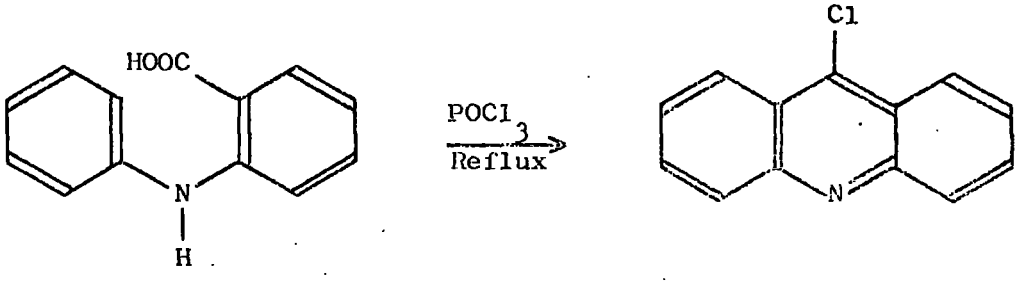


It does not undergo oxidation or reduction in a way analogous to acridine or phenanthridine.

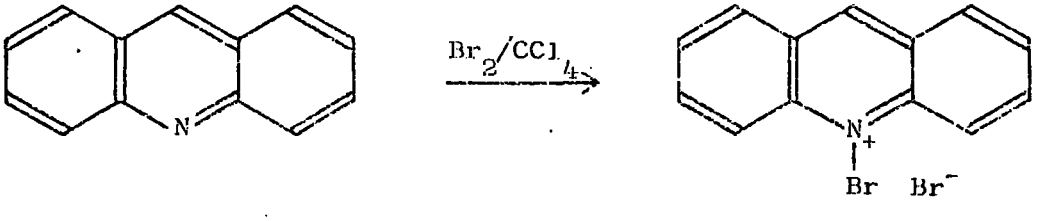
1.2 Early Work on Preparation of Halogenated Derivatives

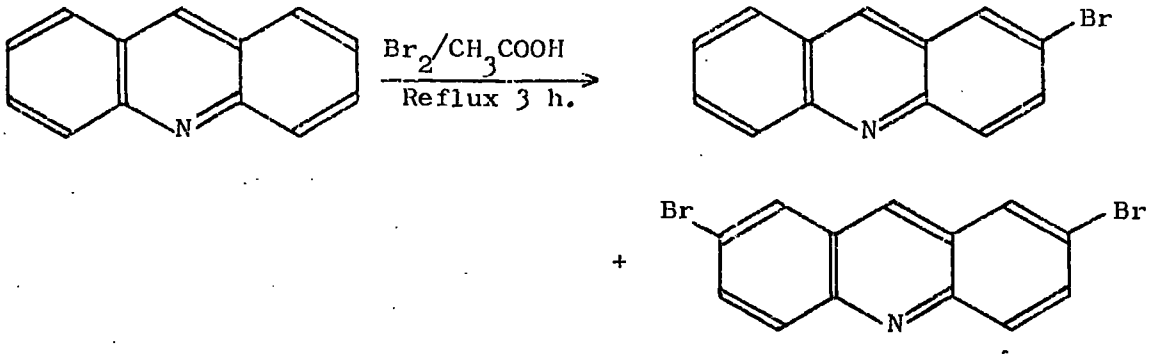
A. Acridines

A wide range of acridines with a chlorine atom in the 9-position have been synthesised, since a standard synthesis of the acridine ring system involves cyclisation, and 9-chloroacridine itself is prepared from diphenylamine-2-carboxylic acid.[159]



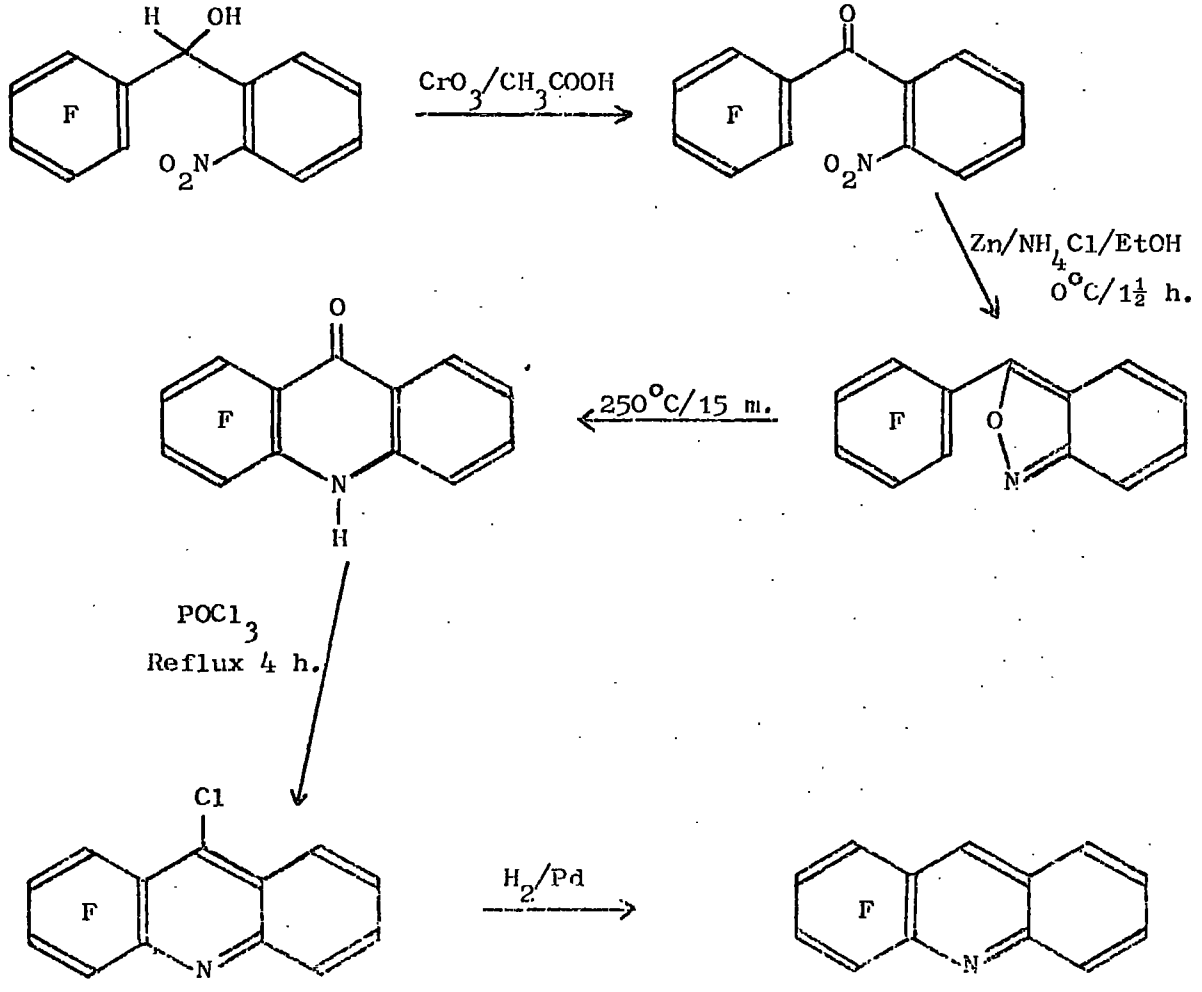
Acridine itself may be brominated with N-bromosuccinimide, in boiling carbon tetrachloride and in the presence of benzoyl peroxide, to give a range of monobromo- and dibromo-acridines, as well as other compounds.[160] The product of elemental bromination depends on the nature of the solvent, and can arise from substitution or addition.[161] In carbon tetrachloride solution, addition occurs to give 10-bromoacridinium bromide, but in acetic acid a mixture of 2-bromoacridine and 2,7-dibromoacridine is produced.



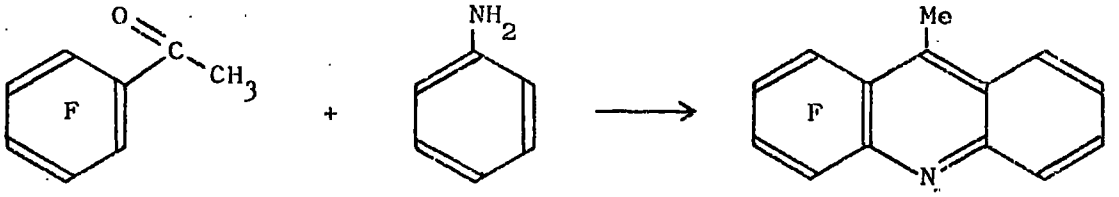


In the case of fluorinated acridines, a whole range of lowly fluorinated compounds has been prepared by cyclisations of suitable diphenylamine-2-carboxylic acids.[162] 1,2,3,4-Tetrafluoroacridine has been prepared in several stages as shown in Figure 2-1, starting from 2,3,4,5,6-pentafluoro-2'-nitrodiphenylmethanol.[163]

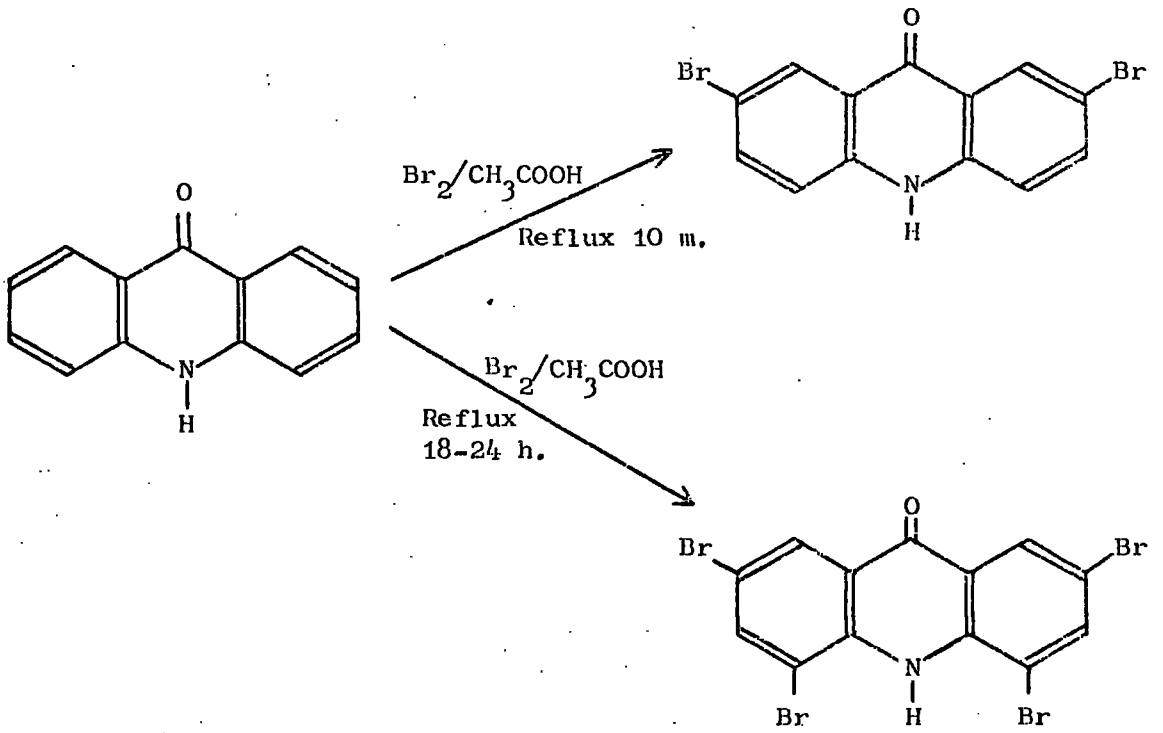
FIGURE 2-1



1,2,3,4-Tetrafluoro-9-methyl acridine has been obtained by reaction between aniline and pentafluorophenylmethyl ketone.[164]

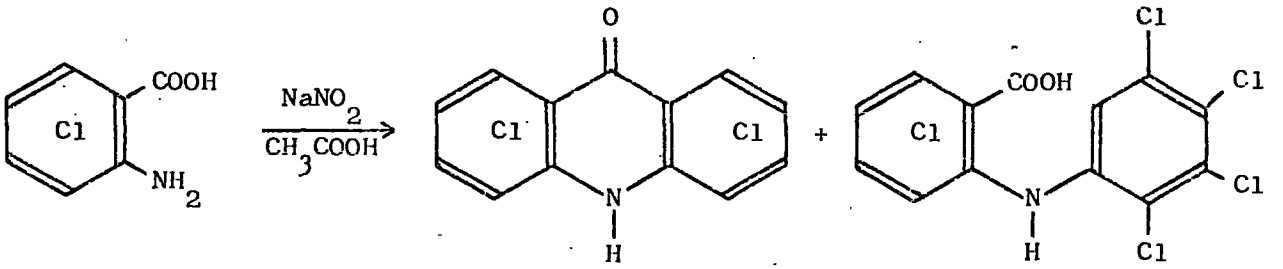


Halogenated 9-acridanones are generally more widely known than halogenated acridines, probably because acridines with a 9-halogen atom are easily hydrolysed to the 9-acridanone, especially when there are other halogen atoms present. When 9-acridanone is treated with elemental bromine in acetic acid solution, 2,7-dibromo-9-acridanone, or 2,4,5,7-tetrabromo-9-acridanone may be isolated, depending upon the severity of the conditions used.[165]

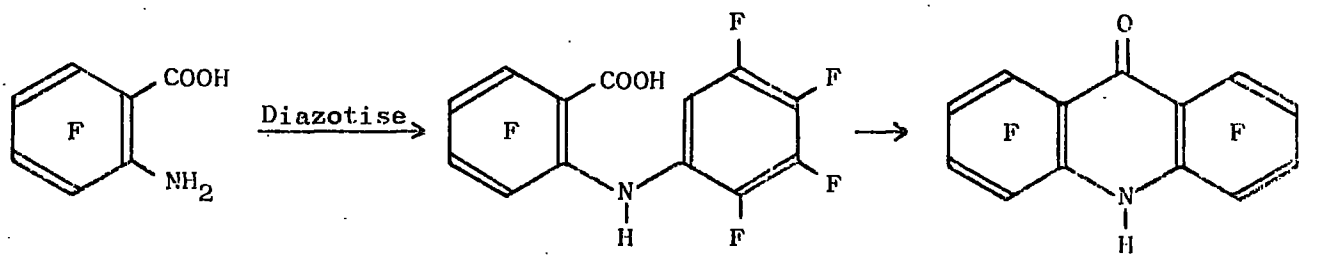


Similar results are obtained when 9-acridanone is reacted with elemental chlorine, but generally milder conditions are needed.[166,167]

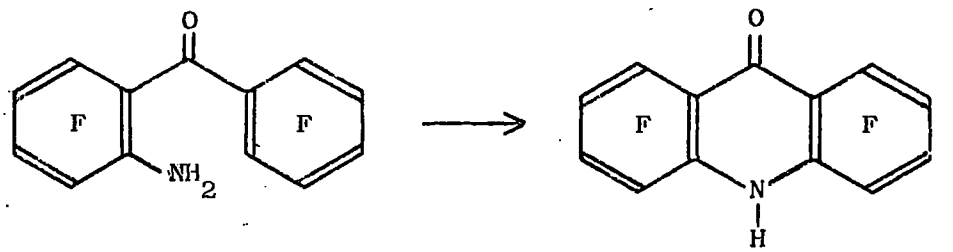
1,2,3,4,5,6,7,8-Octachloro-9-acridanone has been prepared in two ways. As already mentioned, it may be prepared by the direct chlorination of 9-acridanone with antimony pentachloride.[48] The diazotisation of tetrachloroanthranilic acid in acetic acid solution produces 1,2,3,4,5,6,7,8-octachloro-9-acridanone in low yield, together with other compounds.[168]



1,2,3,4,5,6,7,8-Octafluoro-9-acridanone has also been prepared in two ways and the first is analogous to the diazotisation method described above, although a separate cyclisation step is required.[169]



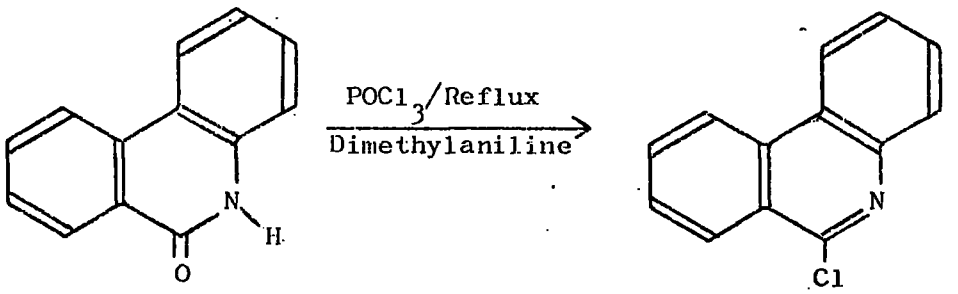
The second method reported is the electrochemical oxidation of 2-aminononafluorobenzophenone.[170]



It is apparent that no exhaustive halogenation of acridine, as opposed to 9-acridanone, has been reported, nor have any very highly halogenated acridines been prepared. Because of its ready availability, 9-chloroacridine seems to be the most convenient starting material for any attempted synthesis of highly chlorinated acridines by the direct chlorination of the acridine ring system.

B. Phenanthridines

No highly halogenated phenanthridines have been reported, nor has any work been described on the halogenation of this ring system. 6-Chloro-phenanthridine, like 9-chloroacridine, is quite well known and is prepared from 6-phenanthridanone.[171]



This seems to be the most suitable starting material for an exhaustive chlorination of the phenanthridine ring system.

C. 7,8-Benzoquinolines

No highly halogenated 7,8-benzoquinolines have been reported nor has any direct halogenation of the ring system been carried out.

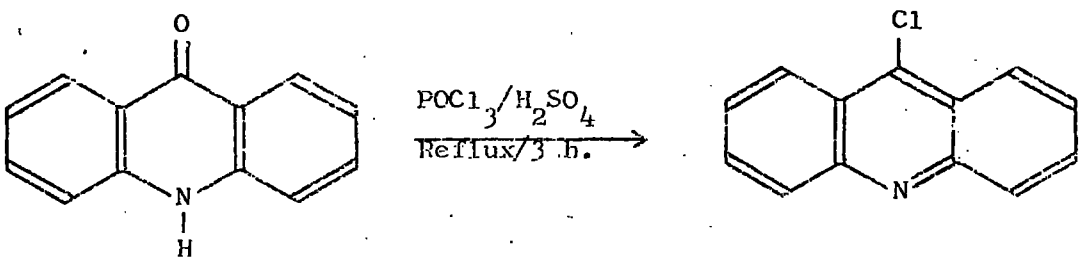
2. Preparation of Starting Materials

2.1 9-Chloroacridine

This was the starting material chosen for the attempted preparation of nonachloroacridine by the direct chlorination of the acridine ring system.

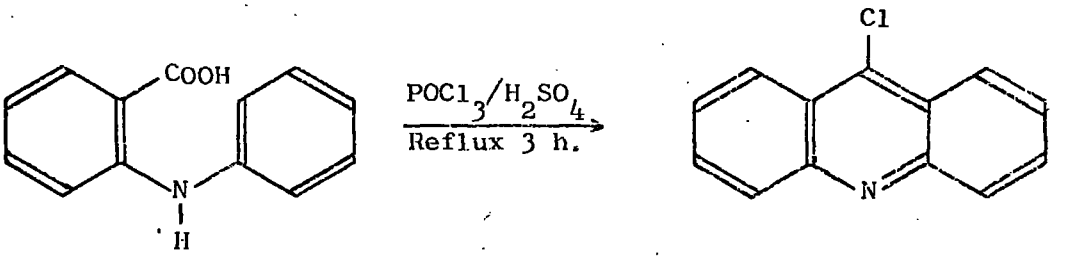
A. Preparation of 9-Chloroacridine from 9-Acridanone

This conversion was carried out by using phosphoryl chloride as reagent, in a procedure similar to that of Graebe and Lagodzinski,[172] the mechanism of which has been investigated by Drozdov.[173] Initially very poor results were obtained, but the addition of a small amount of mineral acid enabled good yields to be achieved.



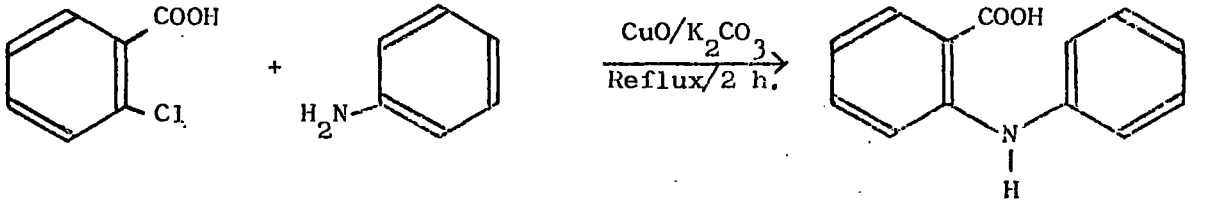
B. Preparation of 9-Chloroacridine from Diphenylamine-2-carboxylic Acid

This was the method most commonly used for the synthesis of 9-chloroacridine and it followed the method of Magidson and Grigorowski,[159] which has been improved by Albert and Ritchie.[174] Phosphoryl chloride was the reagent, but again it was found that a small amount of mineral acid was necessary for good results to be obtained



C. Preparation of Diphenylamine-2-carboxylic Acid

This was prepared by an Ullmann condensation reaction[175] between aniline and 2-chlorobenzoic acid, in the presence of base and with a copper catalyst. Originally the reaction was carried out in iso-amyl alcohol as solvent but this was not very satisfactory and the procedure of Allen and McKee,[176] in which the reaction is carried out in excess aniline, was adopted. Potassium carbonate was used as the base and cupric oxide as catalyst.

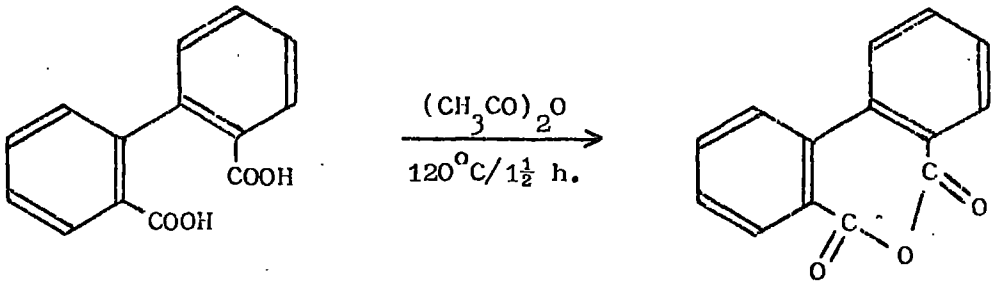


2.2 6-Chlorophenanthridine

This was prepared from diphenic acid, which was first converted to 6-phenanthridanone in three stages, following the procedure of Oyster and Adkins.[177] 6-Chlorophenanthridine was then prepared from 6-phenanthridanone by the method of Badger, Seidler and Thomson.[171]

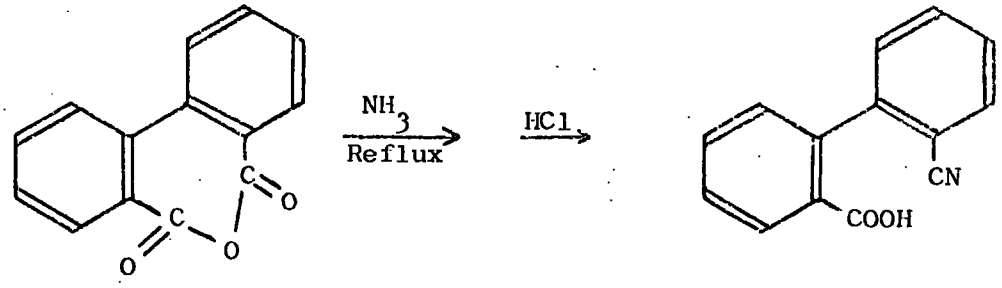
A. Preparation of Diphenic Anhydride from Diphenic Acid

This conversion was achieved simply by heating with acetic anhydride.



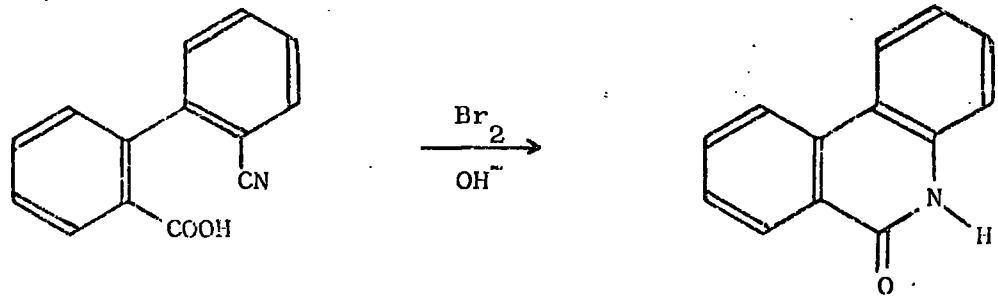
B. Preparation of Diphenamic Acid from Diphenic Anhydride

This conversion was achieved simply by heating with ammonia and then acidifying.



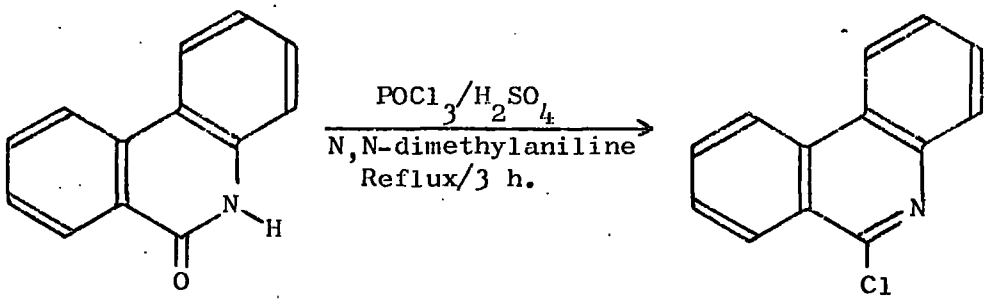
C. Preparation of 6-Phenanthridanone from Diphenamic Acid

This cyclisation reaction was carried out in a reaction which presumably involves hydrolysis to amide and then amine, followed by nitrene formation, by treatment with bromine in alkaline solution.



D. Preparation of 6-Chlorophenanthridine from 6-Phenanthridanone

The method used was that described in the literature[171] in which phosphoryl chloride is used as the reagent, in the presence of some N,N-dimethylaniline. A small amount of mineral acid was also added in an attempt to improve the yields.

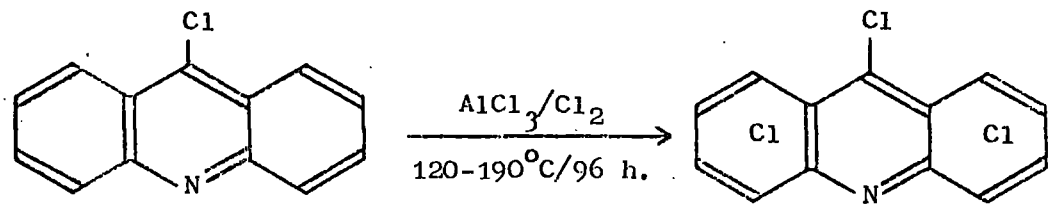


3. Chlorination Reactions

3.1 Chlorination of 9-Chloroacridine

Since all the unchlorinated positions of 9-chloroacridine are in carbocyclic rings, and elemental chlorination with aluminium chloride as catalyst occurs particularly in carbocyclic positions, it might be expected that this method of chlorination would allow nonachloroacridine to be obtained from 9-chloroacridine in one step.

It was found that, provided the reaction time was long enough and the temperature high enough, complete chlorination did indeed occur, and it was possible to use very varying amounts of chlorine.

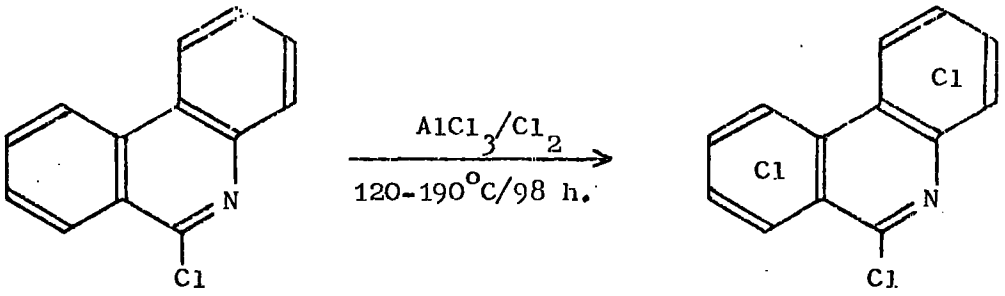


The major difficulty encountered was the ease of hydrolysis of the product to octachloro-9-acridanone, and in early reactions the hydrolysed material formed all, or the majority, of the product. This problem was

overcome by dissolving the residue of the chlorination, which was a complex between nonachloroacridine and aluminium chloride, in dry chloroform and then adding dry methanol. This caused the complex to be broken down and nonachloroacridine was precipitated, since it is much less soluble in chloroform than its complex with aluminium chloride. The mixed chlorides and methoxides of aluminium remained in solution.

3.2 Chlorination of 6-Chlorophenanthridine

Like 9-chloroacridine, all the unchlorinated positions of 6-chlorophenanthridine are carbocyclic, and elemental chlorination, with aluminium chloride as catalyst, gave complete conversion to nonachlorophenanthridine, provided the conditions were made sufficiently forcing.



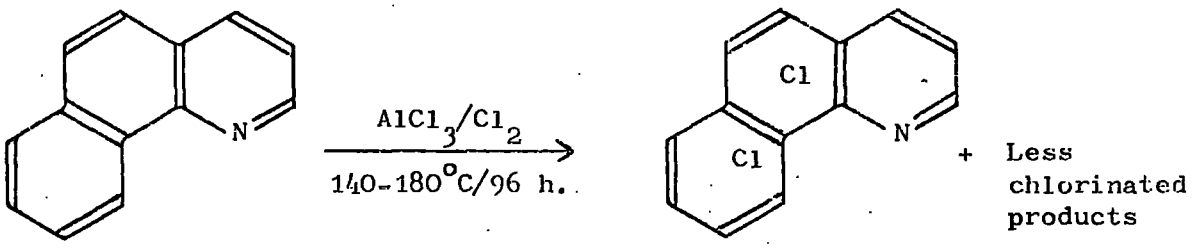
The same method of avoiding hydrolysis was used as for the acridine ring system, but simpler methods were not tried first to see whether the hydrolysis occurred as easily as with acridines. It was necessary to be particularly careful to keep the mixture of chloroform solution and methanol cool, to prevent methanol reacting with nonochlorophenanthridine, giving octachloro-6-methoxyphenanthridine.

3.3 Chlorination of 7,8-Benzoquinoline

A. Aluminium Chloride Catalysed Elemental Chlorination

Unlike 9-chloroacridine and 6-chlorophenanthridine, 7,8-benzoquinoline has three unchlorinated positions in a heterocyclic ring, so aluminium chloride catalysed chlorination would not be expected to replace all the hydrogen atoms in 7,8-benzoquinoline by chlorine. Under the vigorous

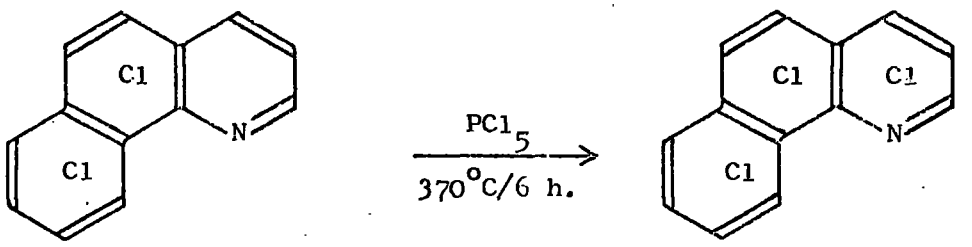
conditions used for the complete chlorination of 6-chlorophenanthridine and 9-chloroacridine, a mixture of mostly hexachloro-7,8-benzoquinoline and pentachloro-7,8-benzoquinoline was obtained from 7,8-benzoquinoline. Presumably chlorination only occurs in the carbocyclic rings.



This product showed no evidence of susceptibility to hydrolysis and could be separated from the complex with aluminium chloride simply by adding to ice water.

B. Further Chlorination with Phosphorus Pentachloride

The further chlorination of the mixture obtained as in section A was attempted by heating with phosphorus pentachloride in an autoclave. There was considerable difficulty in finding the most suitable temperature for the reaction, although it was eventually discovered that reaction at 370°C, in a steel autoclave, gave nonachloro-7,8-benzoquinoline quite cleanly.



This product was also not susceptible to hydrolysis and the phosphorus compounds remaining at the end of the reaction could be removed by hydrolysis with ice-water.

Earlier it had been found that, with lower reaction temperatures an octachloro-7,8-benzoquinoline was produced, suggesting that one of the hydrogen atoms in the ring system is particularly difficult to replace, but it is not

at all obvious which one this is.

With higher temperatures, or if a nickel-lined autoclave was used, some chlorine was added to the ring system causing partial saturation. The use of a steel autoclave, rather than a nickel-lined one, presumably overcomes this problem because iron is a reagent for achieving dechlorinative aromatisation.

CHAPTER III

Properties of Some Perchloroheterocyclic Compounds Containing Nitrogen

1. Fluorination Reactions

The synthesis of fully fluorinated heterocyclic systems from the corresponding fully chlorinated heterocyclic systems, by halogen exchange reactions using potassium fluoride in an autoclave, has been shown to be quite generally applicable, as mentioned in Chapter I. Thus the reaction has been successful for pyridine, diazabenzenes, azanaphthalenes and diazanaphthalenes, but before this work was begun it had not been applied to tricyclic systems.

1.1 Fluorination of Nonachloroacridine

The fluorination of nonachloroacridine was attempted in a nickel-lined autoclave, in the solid phase, using dry potassium fluoride as the reagent. It was hoped that a simple halogen exchange reaction would occur so that nonafluoroacridine could be isolated. In fact, virtually no success was had with this reaction, even though a wide range of conditions and methods of working up the residue were used.

Unlike fluorinations of other perchlorinated heteroaromatic nitrogen compounds, such as pentachloropyridine,[1] no fluorinated substrate could be transferred out of the hot autoclave under vacuum, but only low molecular weight gases, and it was necessary to empty the autoclave and try to extract a product from the residue by some other means.

Vacuum sublimation of this residue, or extraction by a solvent, allowed very small amounts of a mixture shown by its mass spectrum to be chloro-fluoro-9-acridanones, particularly tetrachlorotetrafluoro-9-acridanone, to be obtained. If the inorganic part of the residue was dissolved in water, a black solid remained which was largely polymeric.

There seem, therefore, to be at least two problems involved in the fluorination of nonachloroacridine. First, even under the mildest conditions used, the ring system seems to be unstable and only very small recoveries of tractable material were obtained. Secondly, with all the work-up procedures used, any tractable material remaining is converted to the 9-acridanone, indicating that a 9-fluorine atom is particularly susceptible to hydrolysis.

Since nonachlorophenanthridine is less susceptible to hydrolysis than nonachloroacridine (see section 2.2. below), the second of these problems might be absent in the fluorination of nonachlorophenathridine, so the fluorination of nonachlorophenanthridine was investigated more extensively.

1.2 Nonachlorophenanthridine

A. In a Solvent

The fluorination of nonachlorophenanthridine by caesium fluoride in sulpholane was attempted, using quite varying reagent quantities and temperatures. In all cases, water was used to separate the substrate from sulpholane and caesium salts, and only hydrolysed 6-phenanthridanones were isolated. The degree of fluorination was variable, but never nearly complete, even under the most vigorous conditions possible in this sort of solvent system. However, recoveries of material were quite good, indicating that not much breakdown of the ring was occurring.

B. In the Solid Phase

The fluorination of nonachlorophenanthridine, with potassium fluoride in an autoclave, was attempted under a range of reaction conditions, including quite low temperatures and short reaction times. In no case was it possible to transfer any substrate, under vacuum, out of the hot autoclave, and only low-molecular weight gasses were obtained in this way, so it was necessary to open the autoclave and try to isolate material from the residue in some other way.

In fact, it was not possible to obtain any tractable material from any reaction, indicating that extensive decomposition of the phenanthridine ring system occurred.

It seems that the acridine and phenanthridine ring systems have some feature which makes them break down when solid phase fluorinations of their perchlorinated derivatives are attempted. It may be that this feature is the presence of a heterocyclic, nitrogen containing, ring to which two benzene rings are fused, for these are the first examples of perchlorinated systems with this feature. Nonachloro-7,8-benzoquinoline, however, has only one carbocyclic ring fused to the heterocyclic ring so, if it is the presence of two fused rings on the heterocyclic ring which causes decomposition, it should be possible to fluorinate nonachloro-7,8-benzoquinoline quite smoothly.

1.3 Nonachloro-7,8-benzoquinoline

The fluorination of nonachloro-7,8-benzoquinoline with potassium fluoride in an autoclave was attempted using both the conditions which are successful with heptachloroquinoline, and the much milder conditions which failed with nonachloroacridine and nonachlorophenanthridine.

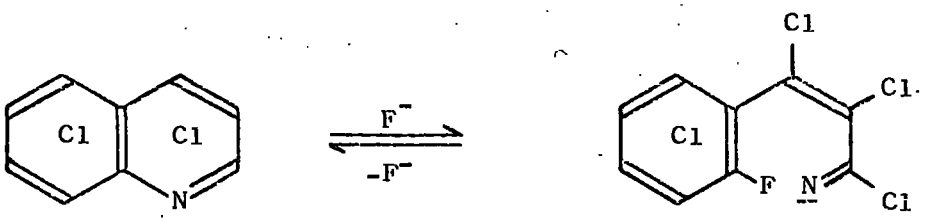
With this ring system, too, it was not possible to obtain any tractable compound, apart from a highly degraded mixture, under either of the reaction conditions used. This was despite the fact that several ways of isolating workable material from the reaction residue were attempted.

1.4 General Conclusion

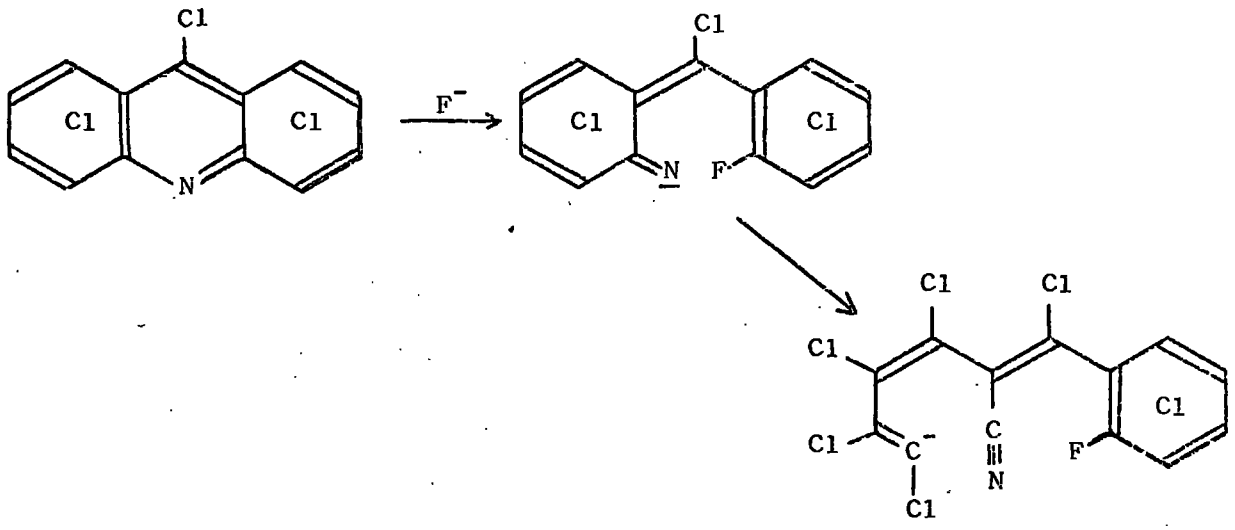
It is clear that the attempted fluorination in an autoclave, of all these three chlorinated systems is not at all successful, because there is some way in which these systems can decompose, which is not possible with pentachloropyridine, heptachloroquinoline, heptachloroisoquinoline or hexachlorophthalazine. These three systems which decompose all have three fused rings, with a hetero atom, and it is quite possible that it is this

presence of three fused rings which is necessary for decomposition to occur. There are at least two ways in which decomposition might occur more readily for a three-ring system, than for a two-ring system.

First, attack by fluoride ion may occur at a bridgehead position at any stage of the fluorination. With heptachloroquinoline, such an attack produces an anion which can do little but recyclise, so that attack at a bridgehead position is reversible for a two-ring system:

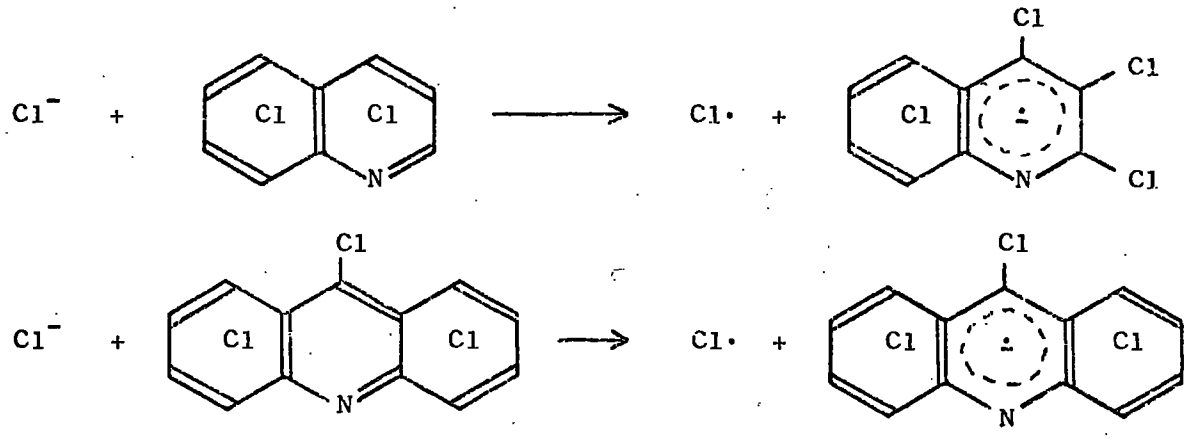


With nonachloroacridine, such an attack produces an anion which can undergo further rearrangements in the third ring, so that attack at a bridgehead position is irreversible for a three-ring system.



Since this process could occur at any stage in the fluorination, attack at bridgehead positions can explain why the fluorination of chlorinated systems with three fused rings fails under conditions which are suitable for systems with two fused rings.

Secondly, systems with three fused rings are better electron acceptors than systems with two fused rings, and there are weak electron donors, such as chloride or fluoride ions present, so that radical anions may be produced. For heptachloroquinoline and nonachloroacridine the reactions would be:



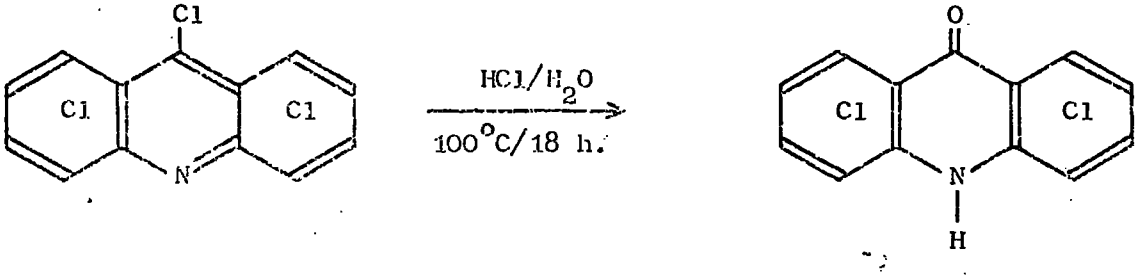
Once formed, the radical ions could decompose by a variety of means, producing a mixture of degraded material. Because the three-ring systems are better electron acceptors than the two-ring systems, this electron transfer process can also explain why the fluorination of chlorinated systems with three fused rings fails.

2. Hydrolysis Reactions and Basicity

2.1 Nonachloroacridine

A. Hydrolysis

As mentioned in Chapter II, nonachloroacridine is readily hydrolysed to octachloro-9-acridanone and, by using hydrochloric acid, it was possible to isolate a pure sample of octachloro-9-acridanone.

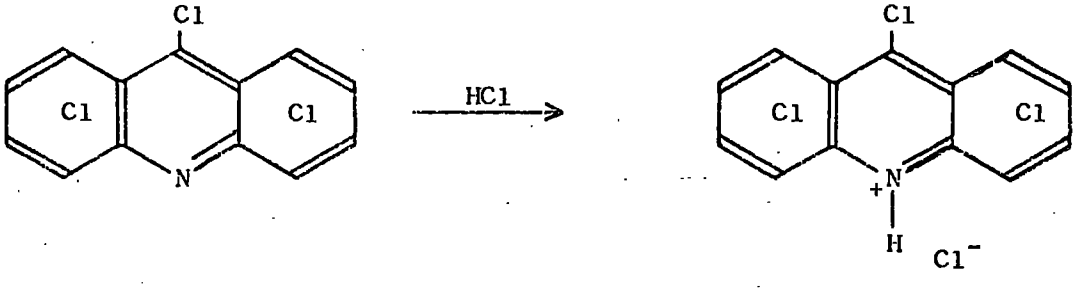


The molecular weight and analytical data show that the product is a monohydroxyoctachloroacridine, but do not demonstrate at which position hydrolysis has occurred. That it has occurred in the 9-position is indicated by the carbonyl and N-H peaks in the infra-red spectrum, by the similarity of the ultra-violet spectrum to that of 9-acridanone,[178] and by a comparison of the melting point with the values quoted for samples of octachloro-9-acridanone which had been obtained earlier, by unambiguous syntheses.[48,168]

As mentioned in Chapter I, perchlorinated heteroaromatic compounds containing nitrogen would be expected to be more basic, as the number of chlorine atoms ortho to the ring nitrogen atom decreases. As there are no chlorine atoms ortho to the nitrogen atom in nonachloroacridine, it would be expected to be quite basic and this accounts for the very easy hydrolysis, if hydrolysis is an acid induced process.

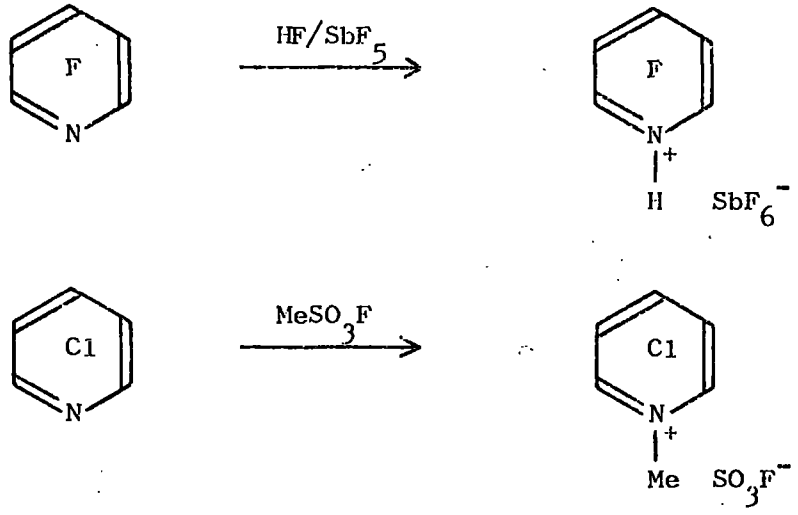
B. Reaction with Hydrogen Chloride Gas

It may be that nonachloroacridine is sufficiently basic to form a salt with hydrogen chloride, and this possibility was investigated by bubbling dry hydrogen chloride gas through a solution of nonachloroacridine. Uptake of gas occurred and a cloudiness developed in solution, which is consistent with the formation of nonachloroacridinium chloride.



However, it was not possible to isolate anything other than nonachloroacridine from the solution. It is possible that more powerfully acidic reagents might allow salts to be isolated, as a mixture of hydrogen fluoride

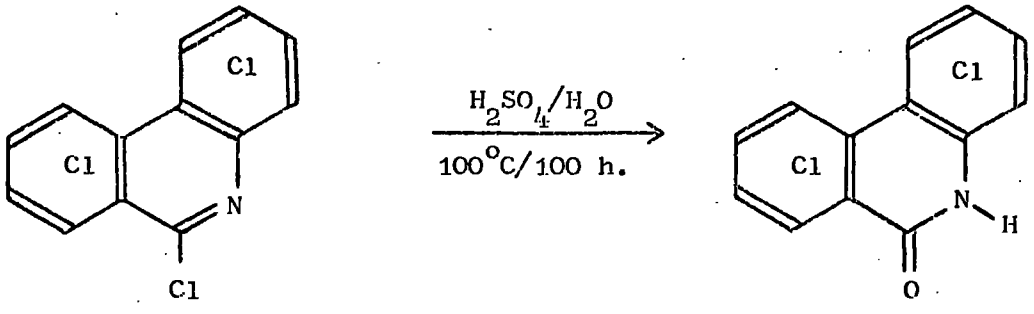
and antimony pentafluoride allows a hexafluoroantimonate salt of pentafluoropyridine to be isolated,[124] and methyl fluorosulphonate allows a salt of pentachloropyridine to be isolated.[179]



2.2 Hydrolysis of Nonachlorophenanthridine

In nonachlorophenanthridine, there is one chlorine atom ortho to the ring nitrogen, so it would be expected to be less basic than nonachloroacridine, and consequently less susceptible to acid induced hydrolysis. Indeed, it was completely unaffected by the conditions which completely converted nonachloroacridine to octachloro-9-acridanone, and this tends to confirm that hydrolysis is an acid induced process.

Using more vigorous conditions, however, it was possible to hydrolyse nonachlorophenanthridine to octachloro-6-phenanthridanone.



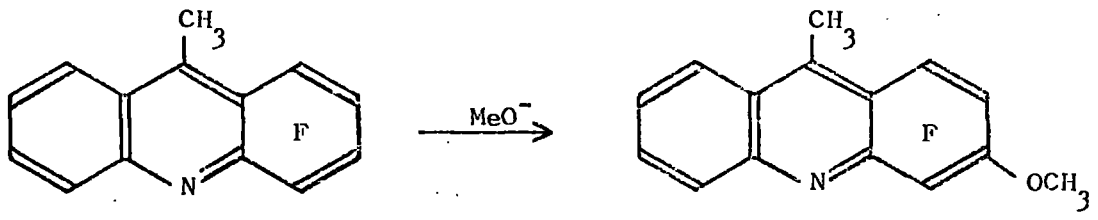
As with the acridine ring system, the molecular weight and analytical data show that the product is a monohydroxyoctachlorophenanthridine, but do not

demonstrate at which position hydrolysis has occurred. However, it is only if hydrolysis is at the 6-position that the compound would be expected to exist as the keto tautomer. The presence of carbonyl and N-H peaks in the infra-red spectrum of the product, taken together with the similarity of its ultra-violet spectrum to that of 6-phenanthridanone imply that the product is indeed octachloro-6-phenanthridanone.

3. Nucleophilic Substitution Reactions

3.1 Nonachloroacridine

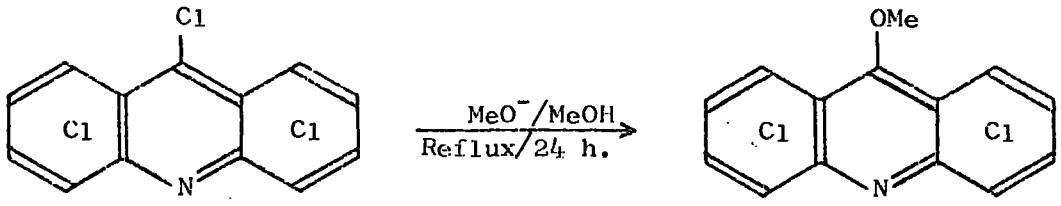
Of the various monochloroacridines, 9-chloroacridine is by far the most susceptible to nucleophilic attack,[180] which suggests that the 9-position is that position which is most activated to nucleophilic attack by the ring system. It has also been shown that 1,2,3,4-tetrafluoro-9-methyl-acridine reacts with nucleophiles, such as methoxide ion, to give substitution in the 3-position.[181]



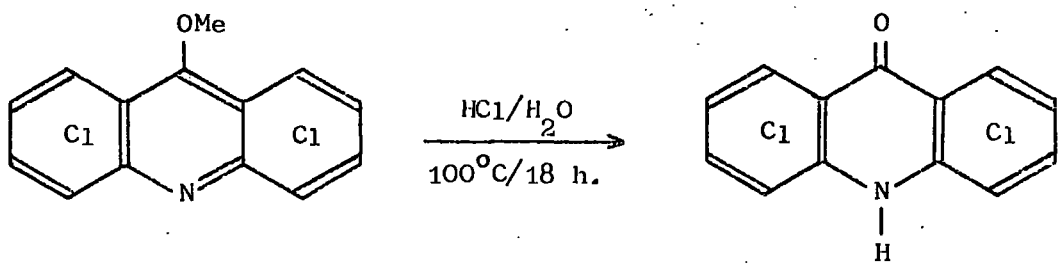
These two facts taken together suggest that nonachloroacridine will undergo nucleophilic attack in the 9-position quite readily, and that then attack might occur in the 3- and 6-positions.

A. Methoxide Ion

(i) One Equivalent Methoxide Ion. Because of the low solubility of nonachloroacridine, this reaction was carried out on a suspension in methanol, but quite mild conditions were sufficient to produce octachloro-9-methoxy-acridine.

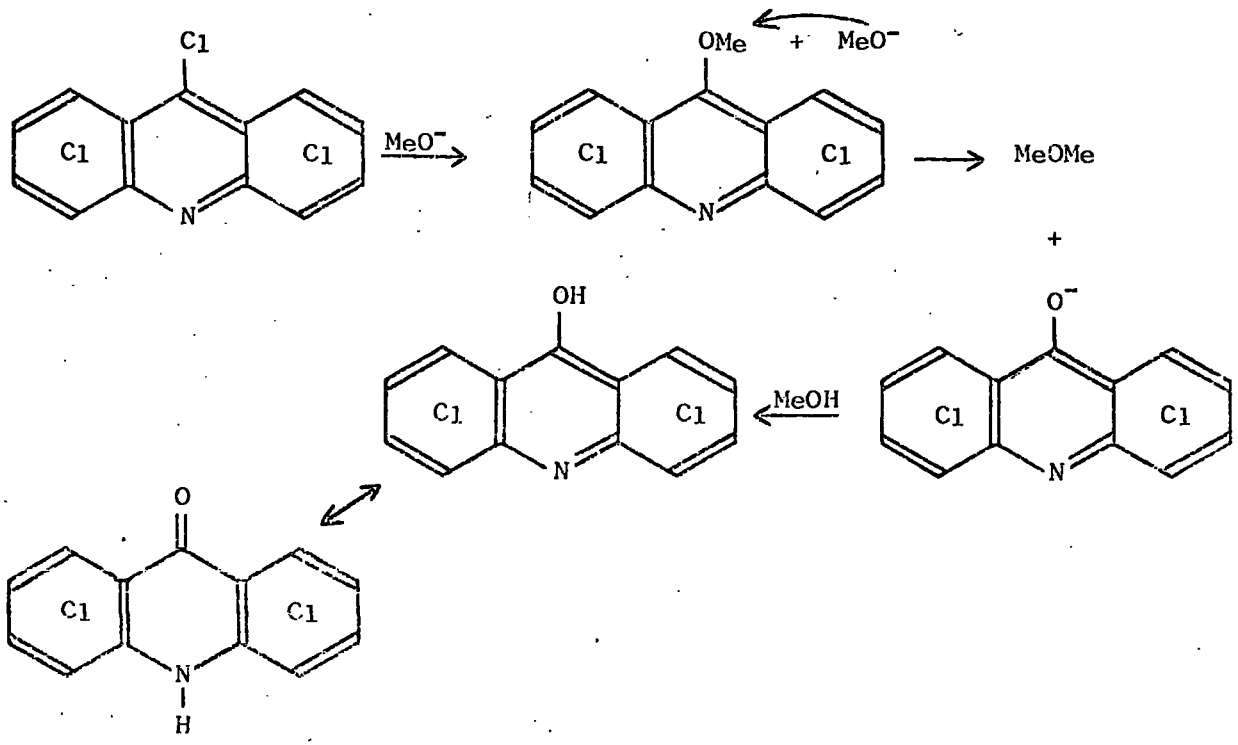


The orientation of the substituent in the product was demonstrated by hydrolysing the methoxy derivative to octachloro-9-acridanone, obtained earlier.



(ii) Two Equivalents Methoxide Ion. Under moderately forcing conditions (prolonged reflux at atmospheric pressure) a second methoxide ion would not react and only octachloro-9-methoxyacridine could be isolated.

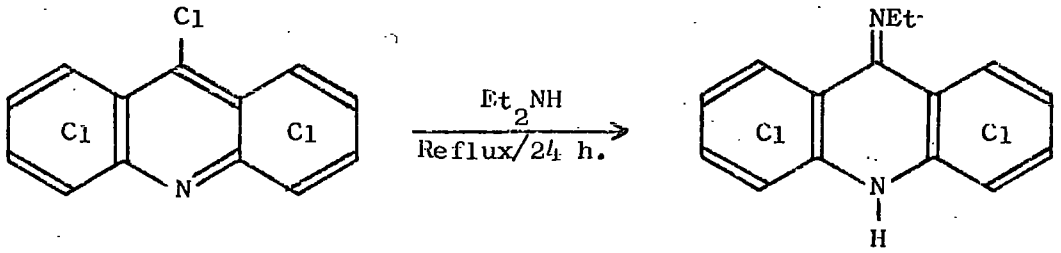
If nonachloroacridine was reacted with methoxide ion under pressure and at high temperatures, octachloro-9-acridanone was obtained, presumably by initial conversion to the monomethoxy derivative followed by attack of another methoxy group on the substituent.



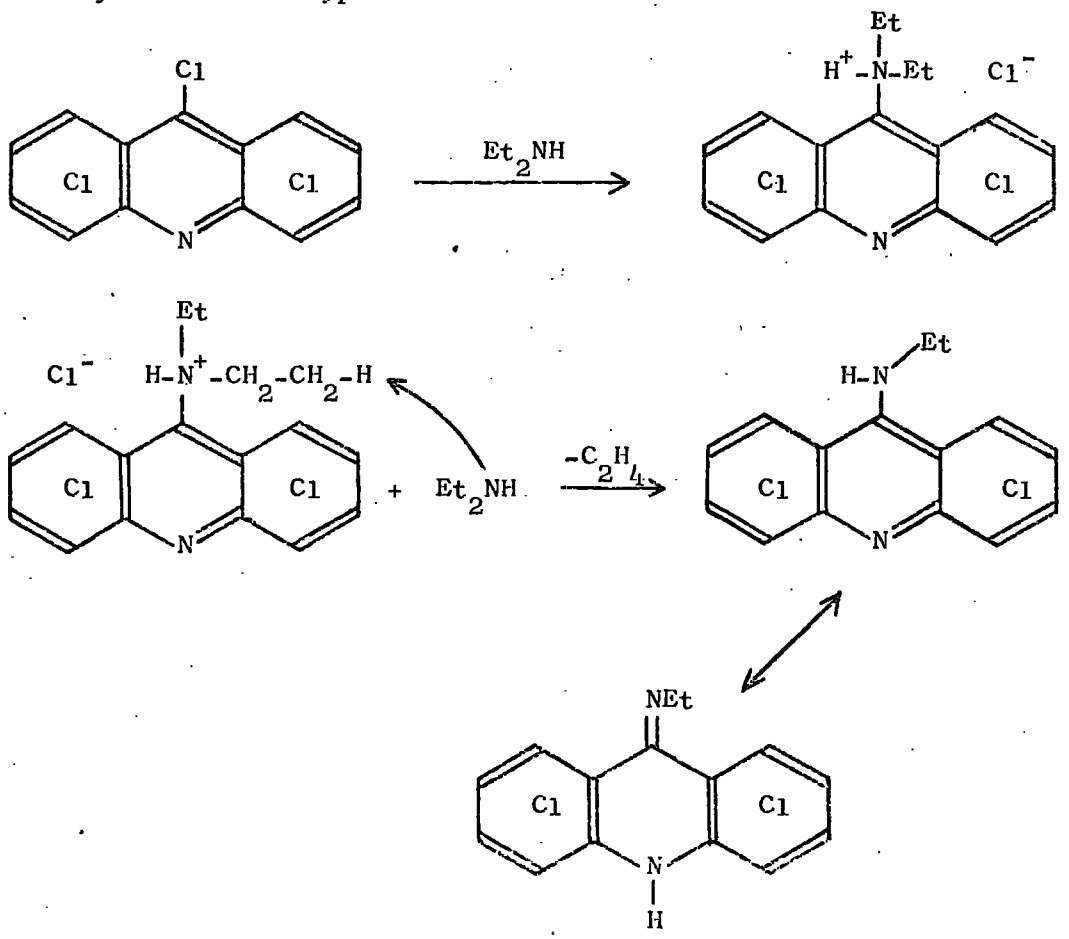
Such a mechanism would release dimethyl ether gas during the reaction, and it was indeed observed that a pressure build up occurred.

B. Diethylamine

Nonachloroacridine reacted with excess diethylamine to give octachloro-9-ethyliminoacridan.

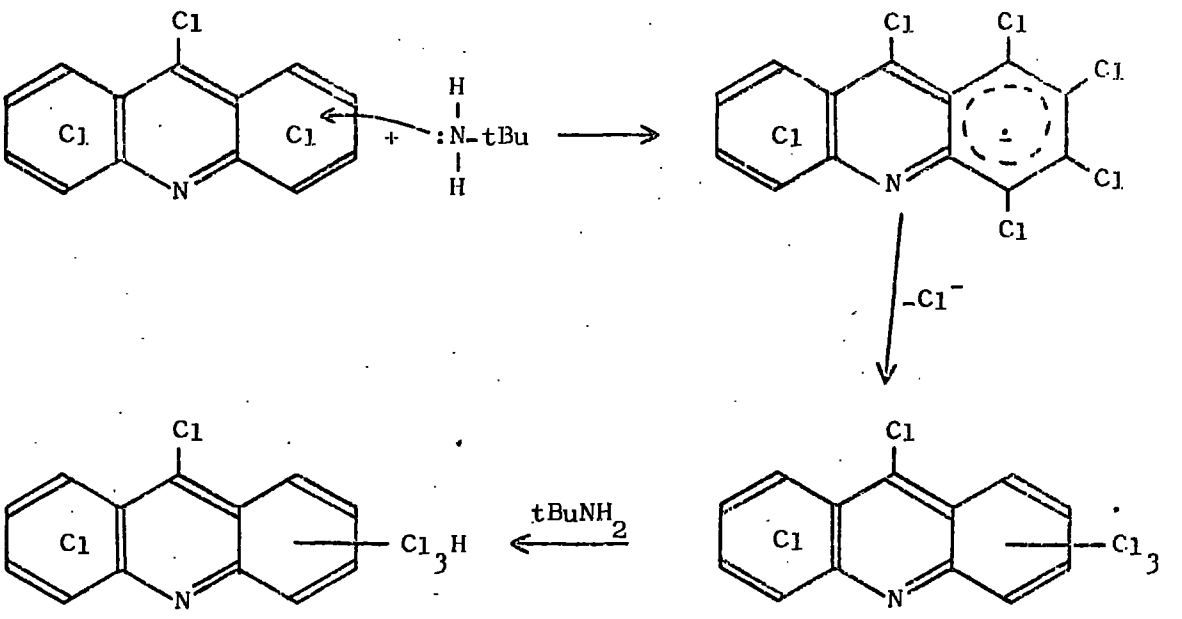


This assignment of the orientation of the substituent in the product is based on a comparison with the methoxide ion reaction, and on the fact that the infra-red spectrum shows that the imino tautomer is present, by the C=N absorbtion. Presumably the mechanism involves simple substitution followed by a Hoffmann type elimination.



C. Reaction with t-Butylamine

Since t-butylamine is such a sterically hindered molecule, it may be difficult for it to react with nonachloroacridine in a simple nucleophilic substitution process. In practice it was found, by the mass spectrum, that the material recovered from reaction of nonachloroacridine with excess t-butylamine contained a lot of starting material, some substitution product, and some octachloroacridines. The latter probably arise by a reductive dechlorination process, which has not been observed before in a thermal reaction, although reductive deiodinations have been reported.[111] The mechanism could involve donation of an electron to the ring system, followed by loss of chloride ion.

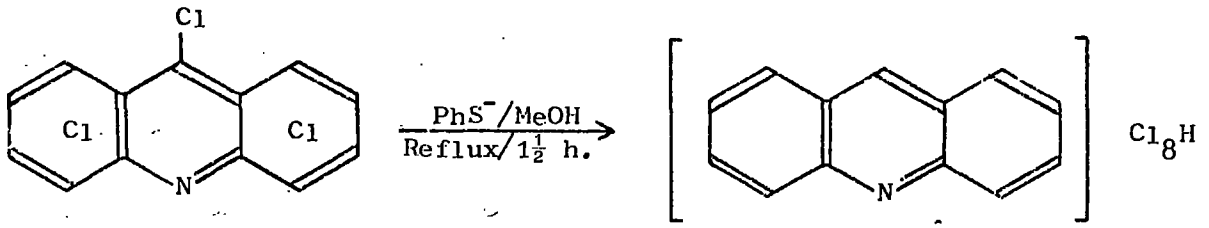


As shown here, thin layer chromatography of the product demonstrated that the reductive dechlorination occurred at several places in the molecule.

D. Thiophenoxide Ion

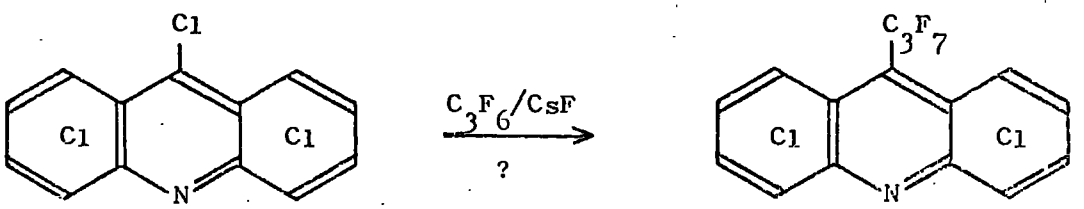
Thiophenoxide ion is larger than methoxide ion, and it is also a better electron donor, so it would be more likely to cause reductive dechlorination than methoxide ion. In practice, nonachloroacridine gave no substitution

with thiophenoxide ion, but only reductive dechlorination, leading to a product mixture containing starting material and octachloroacridines.



E. Hexafluoropropene in the Presence of Fluoride Ion

When caesium fluoride is stirred in a suitable solvent, such as sulpholane, under an atmosphere of hexafluoropropene gas, heptafluoroisopropyl anions are produced, which have been shown to effect substitution reactions in highly fluorinated heteroaromatic compounds.[182,183] It was thought possible that nonachloroacridine might be sufficiently reactive for it to undergo substitution by heptafluoroisopropyl anions



In practice, it was necessary to use water to remove caesium salts and sulpholane after the reaction was finished, and only octachloro-9-acridanone was isolated. This does not necessarily imply that heptafluoroisopropyl anion will not displace chloride from nonachloroacridine, since octachloro-9-heptafluoroisopropylacridine could possibly be hydrolysed as easily as nonachloroacridine.

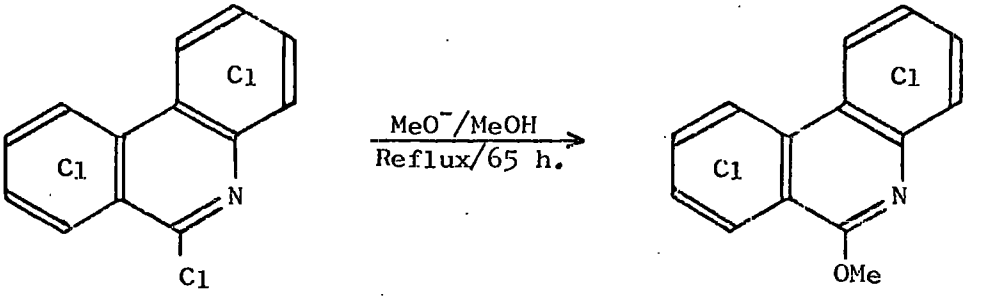
3.2 Nonachlorophenanthridine

The chlorine atom of 6-chlorophenanthridine is found to undergo nucleophilic displacement readily,[184] but not as readily as 9-chloroacridine, indicating that the 6-position is most activated to nucleophilic attack by

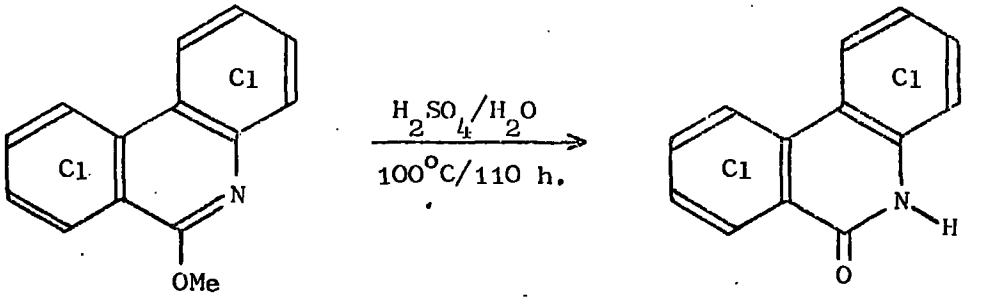
the ring system, and suggesting that nuclecphilic substitution of nonachlorophenanthridine may occur in the 6-position.

A. Methoxide Ion

Because of the low solubility of nonachlorophenanthridine, reaction with methoxide ion was carried out in suspension in methanol, but reaction occurred quite readily, though less readily than in the case of nonachloroacridine. With one equivalent of methoxide ion, octachloro-6-methoxyphenanthridine was produced.

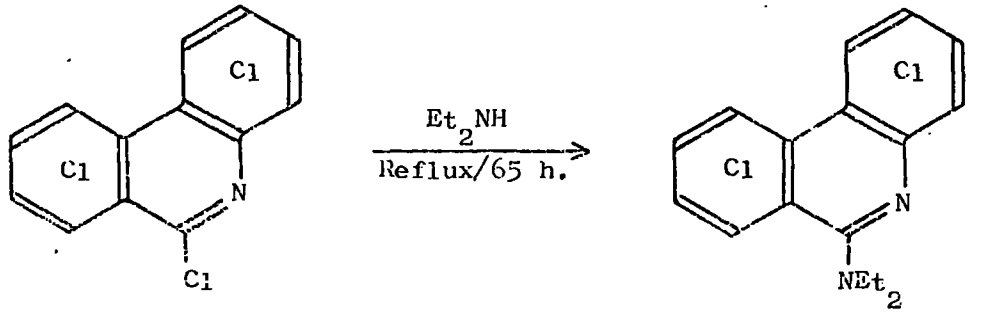


The orientation of the substituent in the product was demonstrated by its hydrolysis to octachloro-6-phenanthridanone, obtained earlier.



B. Diethylamine

Nonachlorophenanthridine reacted with excess diethylamine to give octachloro-6-diethylaminophenanthridine.



In this case, the assignment of orientation rests simply on a comparison with the analogous methoxide ion substitution.

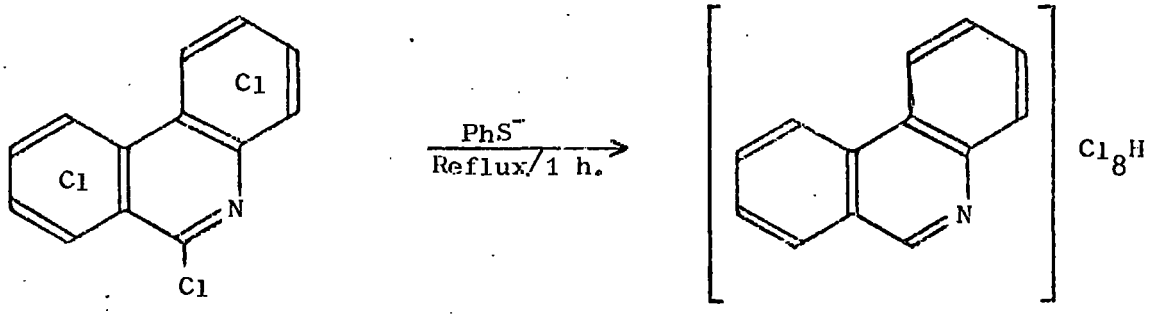
It is interesting that, unlike the corresponding acridine derivative, this phenanthridine derivative does not react further to give an imino phenanthridan.

C. t-Butylamine

Like nonachloroacridine, nonachlorophenanthridine is not very reactive towards t-butylamine and simple substitution is not the only reaction process. The material isolated was a mixture of substituted phenanthridines, starting material, octachloro-6-phenanthridanone, and partially dechlorinated phenanthridines, indicating that, with this bulky amine, reductive dechlorination is an important process.

D. Thiophenoxide Ion

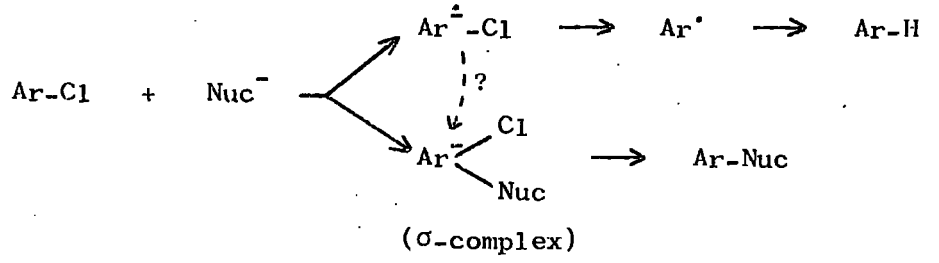
Like nonachloroacridine, nonachlorophenanthridine does not react with thiophenoxide ion by a nucleophilic substitution process, but rather by reductive dechlorination, because of the size and electron donor ability of the thiophenoxide anion. Reaction of nonachlorophenanthridine with one equivalent thiophenoxide ion in methanol, gave a mixture of starting material and octachlorophenanthridines.



3.3 The Competition between Nucleophilic Substitution and Reductive Dechlorination

The above examples are the first cases where reductive dechlorination competes successfully with nucleophilic substitution in a thermal process,

believed to involve the chlorinated radical anion. Evidence for this mechanism comes in a recent review,[185] where the existence of aromatic radical anions has been described, as well as electron transfers to chlorinated compounds, followed by loss of chloride ions. When a nucleophile reacts with an aromatic chlorine compound to give substitution or reduction, the reaction paths must divide at some point.



(σ-complex)

It is not clear whether the radical anion intermediate for reduction is the first step in the formation of the σ-complex, which is the intermediate for substitution, or whether these two intermediates are interconvertible.

Clearly, the relative stabilities of the two intermediates will determine which of the two processes is favoured in any particular case. If substitution does not proceed via the radical anion, then reduction will be favoured as the donor ability of the nucleophile is increased.

Now, with nonachloroacridine and nonachlorophenanthridine, methoxide ion gives substitution whereas thiophenoxide ion gives reduction, and diethylamine gives substitution whereas t-butylamine gives substitution and reduction. In the case of octachloronaphthalene (see Chapter IV), methoxide ion gives no reaction, diethylamine and t-butylamine give only reduction, and ammonia gives reduction and some substitution.

Thiophenoxide ion is probably a better one-electron donor than methoxide ion, but it is also more nucleophilic and larger, so it is not possible to predict how the relative amounts of reduction and substitution will change when the nucleophile is changed from methoxide to thiophenoxide, whether

substitution proceeds via the radical anion or not. For nonachloroacridine and nonachlorophenanthridine, reduction is much more favoured with thiophenoxide than with methoxide, but this does not really give any information on whether or not the radical anion lies on both reaction paths.

Steric crowding will destabilise σ-complexes, favouring reduction, and this may be illustrated by the way larger amines give reduction with nonachloroacridine and nonachlorophenanthridine, rather than substitution. However, the better one-electron donor ability of the larger amines may also be an important factor here.

Octachloronaphthalene is probably a worse electron acceptor than nonachloroacridine or nonachlorophenanthridine, so radical anions derived from it would be less stable. However, with diethylamine, octachloronaphthalene gives reduction, whereas nonachloroacridine and nonachlorophenanthridine give substitution. This must be because the σ-complex for octachloronaphthalene is considerably less stable than the corresponding σ-complexes for nonachloroacridine and nonachlorophenanthridine.

Overall, the available evidence does not clearly indicate whether the radical anion is on the reaction path to substitution or not, but the fact that in many substitution reactions there is no evidence for any reduction implies that the reaction pathways are completely different.

4. Reactions with Organometallic Reagents

Generally, the reactions of these perchlorinated heterocyclic systems with organometallic reagents have been rather irreproducible and it is difficult to make any rationalisations about the reactions which occur. An obvious possible cause of the irreproducibility is the organometallic reagent used, which was normally n-butyl lithium in n-hexane. While it is not possible to know what impurities might have been present in the reagent, its concentration was measured by a titration procedure. In this procedure

a portion of the solution of the reagent was added to water, and then the mixture was titrated against standard sulphuric acid, using phenolphthalein as indicator. This titration gives the total lithium content of the solution. Another portion of the solution was added to freshly distilled benzyl chloride, water was then added and a titration was carried out as before. This titration gives the non-organometallic lithium content of the solution, because benzyl chloride reacts with the n-butyl lithium.

$$\text{n-BuLi} + \text{PhCH}_2\text{Cl} \longrightarrow \text{n-BuCl} + \text{PhCH}_2\text{Li}$$

$$\text{PhCH}_2\text{Li} + \text{PhCH}_2\text{Cl} \longrightarrow \text{LiCl} + (\text{PhCH}_2)_2$$

$$\text{n-BuLi} + \text{PhCH}_2\text{Cl} \longrightarrow \text{LiCl} + \text{Ph(CH}_2)_4\text{CH}_3$$

The difference between the two titration results hence gives the concentration of the organometallic reagent, n-butyl lithium, in the solution.

4.1 Nonachloroacridine

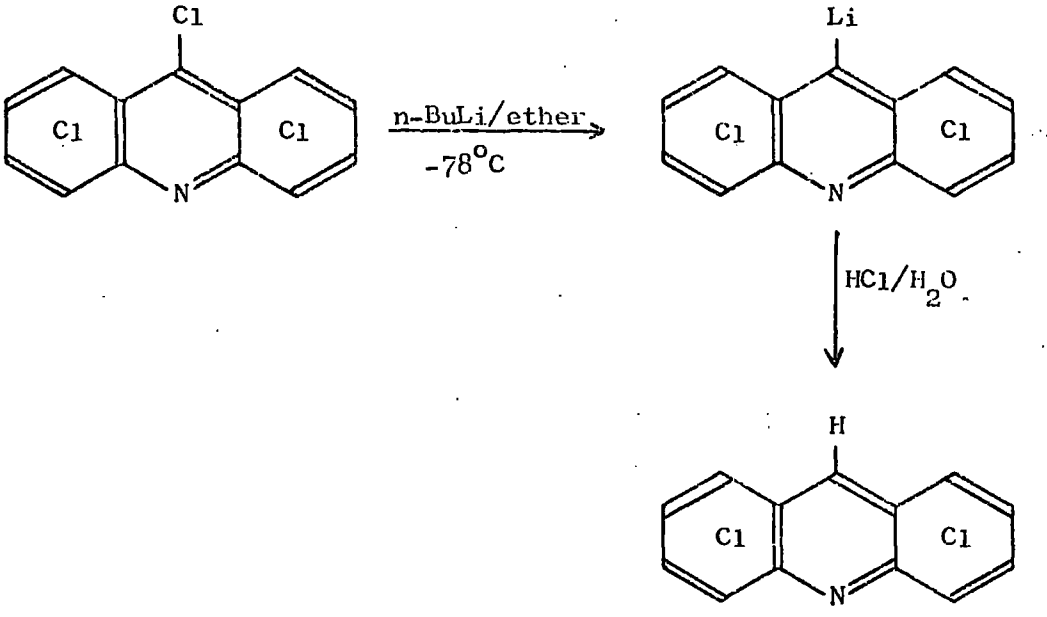
A. Reaction with n-Butyl Lithium

Nonachloroacridine has been reacted several different times, with several different samples of n-butyl lithium and various different observations have been made.

In many reactions, nonachloroacridine was recovered unchanged, even when the reaction was carried out at quite high temperatures and the activity of the n-butyl lithium had been demonstrated by standardisation. The most likely cause of this is that the n-butyl lithium, in this sample, is in some degree of co-ordination which prevents it from being readily reactive with a molecule such as nonachloroacridine, which is quite sterically crowded.

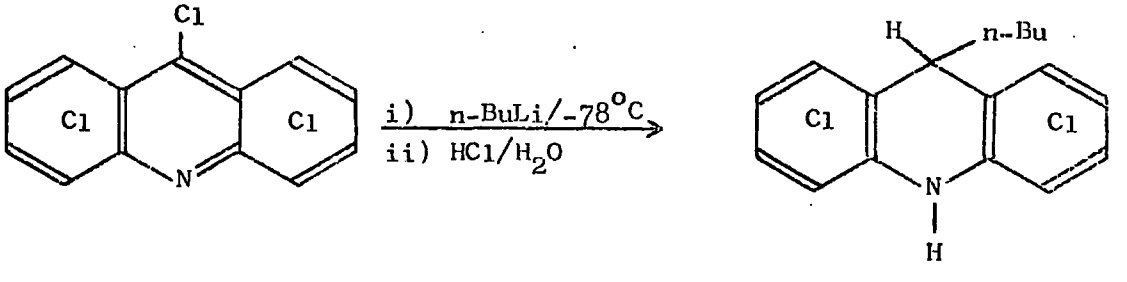
In another reaction, where the reaction mixture was hydrolysed at low temperature, 1,2,3,4,5,6,7,8-octachloroacridine was produced, which is the product expected by a metallation reaction analogous to that observed with

pentachloropyridine.[131,132]



It is interesting that, although this reaction was obtained with a different sample of n-butyl lithium to that which gave no reaction, the concentration of the two samples was very similar. The orientation of the hydrogen atom in the product was demonstrated by the failure of this compound to be hydrolysed by the same conditions as those which convert nonachloroacridine to octachloro-9-acridanone.

In a third type of reaction, where the reaction mixture was hydrolysed at low temperature, 9-n-butyl-1,2,3,4,5,6,7,8-octachloroacridan was produced in very low recovery.



It seems as if, in this case, not only has metallation occurred, but also alkylation, which is the normal reaction for perfluorinated compounds. The n-butyl lithium used for this reaction was much less concentrated than that used in the previous two cases.

There does not seem to be any simple rationale for this diversity in reaction types, but impurities in the n-butyl lithium and varying degrees of its complexation are presumably important factors.

B. Reaction with Phenyl Magnesium Bromide

Like pentachloropyridine,[150] nonachloroacridine does not seem to be sufficiently active to combine with Grignard reagents, and only starting material was recovered when nonachloroacridine was treated with phenyl magnesium bromide, even when the mixture was refluxed in diethyl ether.

4.2 Reaction of Nonachlorophenanthridine with n-Butyl Lithium

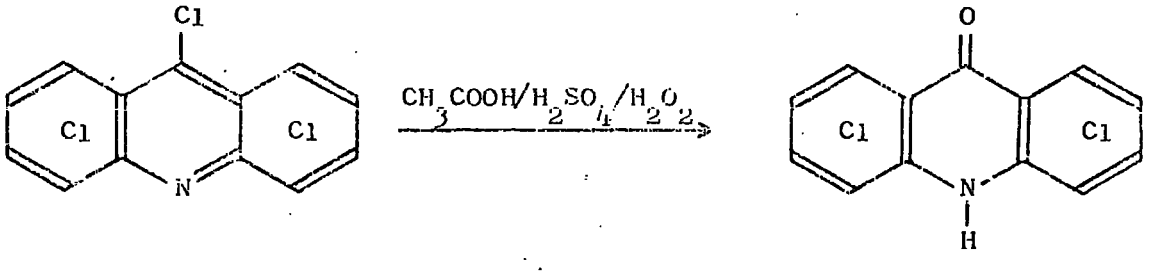
Many reactions between nonachlorophenanthridine and n-butyl lithium, with the temperatures ranging from -78°C to refluxing ether, were attempted, but in all cases only starting material was isolated when the mixture was hydrolysed. All these reactions were done with the same sample of n-butyl lithium as gave no reaction with nonachloroacridine, which nevertheless had quite a high organometallic reactivity when titrated as described above. This tends to confirm that this sample of n-butyl lithium has the molecules complexed in some way which reduces their reactivity.

5. Oxidation and Reduction Reactions

5.1 Nonachloroacridine

A. Oxidation

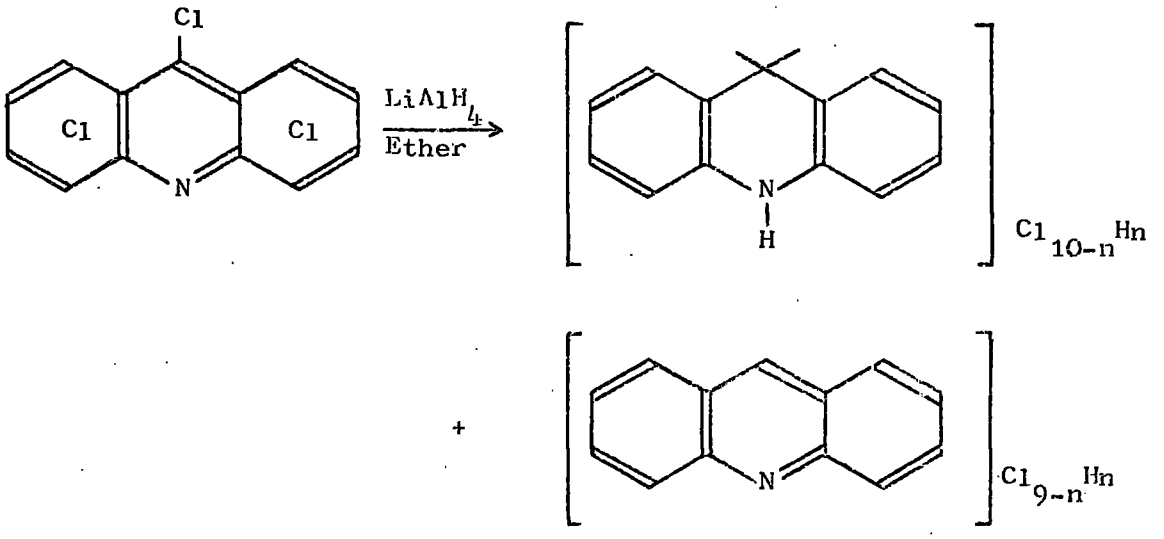
The oxidation of nonachloroacridine to its N-oxide, using acetic acid, sulphuric acid and hydrogen peroxide, as described by Chivers and Suschitzky,[151,152] was attempted. In practice, however, octachloro-9-acridanone was obtained instead, which is not really surprising under these strongly acid conditions.



Because most reagents for preparaing N-oxides use acidic conditions, it will probably not be possible to obtain an N-oxide of nonachloroacridine.

B. Reduction

(i) Using Lithium Aluminium Hydride. When nonachloroacridine was treated with lithium aluminium hydride in diethyl ether, extensive reduction to a mixture of non-fully chlorinated acridines and acridans occurred.

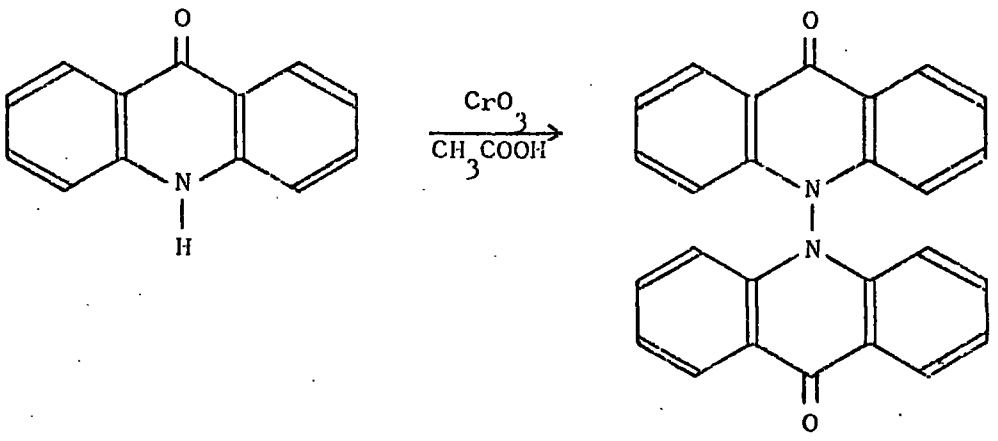


It was not possible to isolate any single compound from the mixture, which also seemed to contain species in which solvent ether had been incorporated into the molecule.

(ii) Using Sodium Borohydride. Since sodium borohydride is a milder reducing agent than lithium aluminium hydride, it was hoped that its reaction with nonachloroacridine might be less complicated and allow single compounds to be isolated. In practice, it was found that the reagent is too mild, and only starting material was recovered from the reaction between sodium borohydride and nonachloroacridine in diethyl ether.

5.2 Oxidation of Octachloro-9-acridanone

It has been reported that oxidation of 9-acridanone with dichromate in hot acetic acid produces 10,10'-di-9-acridanone.[186]

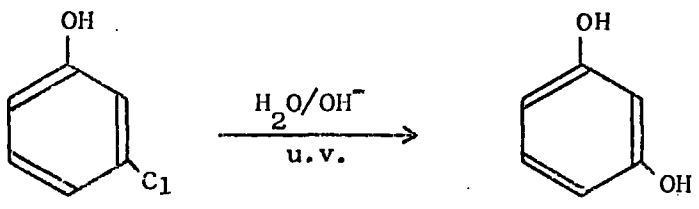


The same reaction was attempted with octachloro-9-acridanone but, even using somewhat more vigorous conditions than those reported for the hydro compound, only starting material was isolated.

6. Pyrolysis and Photolysis Reactions

6.1 Photolysis of Nonachloroacridine in Methanol

As mentioned in Chapter I, photolysis of perchlorinated heteroaromatic compounds frequently proceeds by breakage of a carbon to chlorine bond and photochemically induced reductive dechlorination occurs.[153] However, if a powerful nucleophile is present in the solution, then photochemically induced nucleophilic substitution may occur, and meta-chlorophenol has been converted to meta-dihydroxybenzene by photolysis in aqueous alkali.[187]

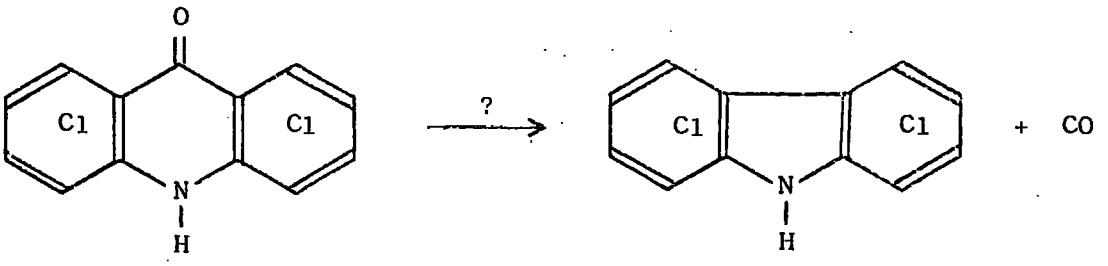


The irradiation of nonachloroacridine in methanol was attempted to see if either of these two processes would occur, but it is unlikely that methanol is sufficiently reactive to give photochemically induced nucleophilic substitution, because it gives no reaction with 3-fluoro-4-methoxynitrobenzene.[188] In fact, no reaction occurred and nonachloroacridine was

recovered unchanged.

6.2 Octachloro-9-acridanone

The mass spectrum of octachloro-9-acridanone shows some evidence for fragmentation occurring by loss of carbon monoxide, so pyrolysis and photolysis reactions were chiefly directed towards the possibility of converting octachloro-9-acridanone to octachlorocarbazole.



A. Pyrolysis

(i) Under Atmospheric Pressure. When octachloro-9-acridanone was heated to the highest temperatures which could reasonably be obtained under atmospheric pressure, it was completely unaffected and was recovered unchanged.

(ii) In an Autoclave. When octachloro-9-acridanone was heated in an autoclave to a temperature which was not much higher than that used in (i) above, extensive decomposition occurred and no tractable material was isolated.

B. Photolysis

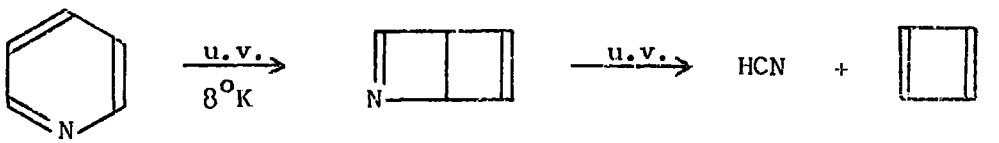
(i) In an Inert Solvent. Photolysis of octachloro-9-acridanone, in an inert solvent and in the region of the spectrum which excites the carbonyl group, might also lead to loss of carbon monoxide. However, when the photolysis was carried out in dry benzene, no reaction occurred and starting material was recovered.

(ii) In Isopropanol. Although photolysis of octachloro-9-acridanone in

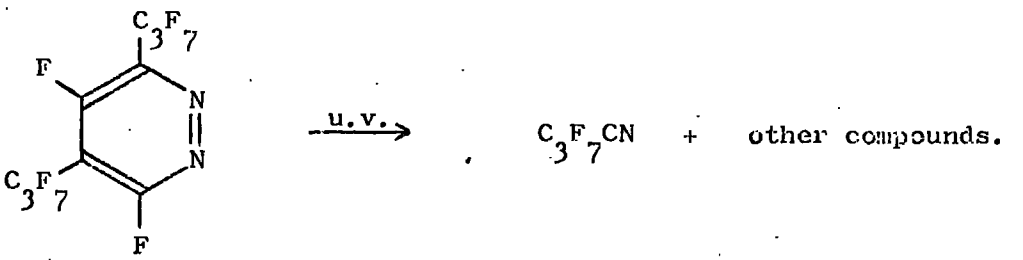
an inert solvent did not cause decarbonylation, it was hoped that some other reaction might occur when the substrate was photolysed in a protic solvent. However, when the photolysis was carried out in isopropanol, it was again observed that no reaction occurred and octachloro-9-acridanone was recovered.

6.3 Pyrolysis of Nonachlorophenanthridine

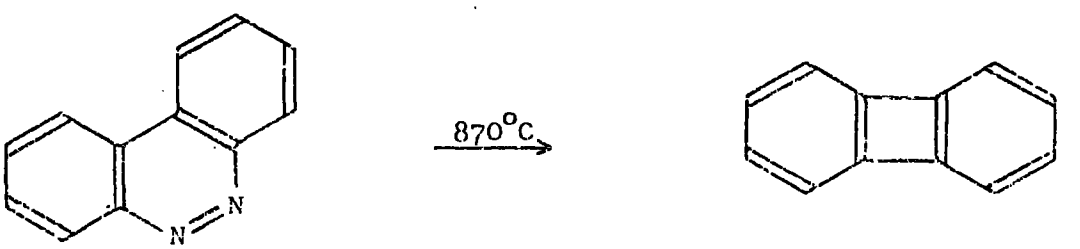
There have been several reports of nitrilic compounds being eliminated from heterocyclic systems. For example, irradiation of a pyridine matrix in argon produces cyclobutadiene by loss of hydrogen cyanide from a valence bond isomer.[189]

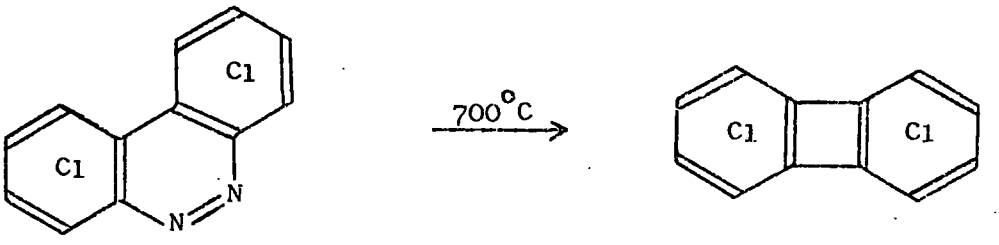


Also, perfluoroisobutyrylnitrile is one of the products when perfluoro-3,5-bisisopropylpyridazine is irradiated.[190]

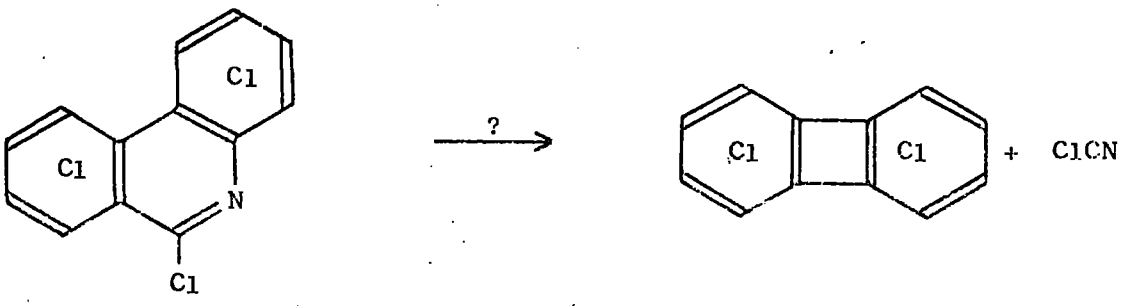


It has also been reported that pyrolysis of benzo[c]cinnoline and octachlorobenzo[c]cinnoline causes loss of nitrogen and leads to the formation of biphenylene and octachlorobiphenylene, respectively.[191]

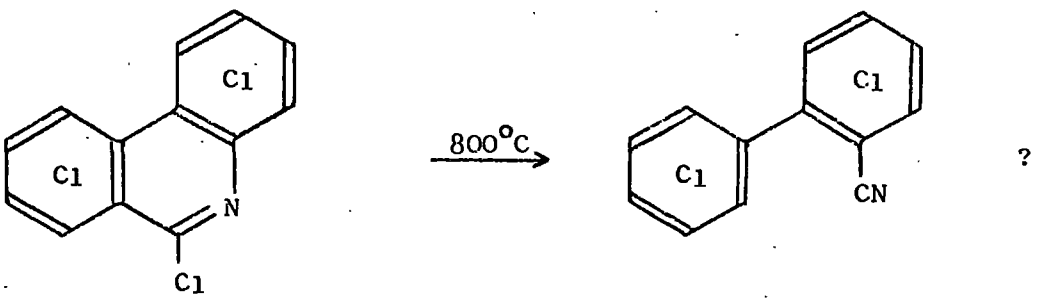




On the basis of all these observations, it was hoped that pyrolysis of nonachlorophenanthridine might cause loss of cyanogen chloride, with the formation of octachlorobiphenylene.



In practice, the product of hydrolysis had the same molecular weight as nonachlorophenanthridine, but the infra-red spectrum was very similar to that of decachlorobiphenyl, and seemed to show a weak C≡N absorbtion. At the time of writing it is not clear what the product of pyrolysis is, although it may be nonachlorobiphenyl-2-cyanide.



Preliminary attempts to hydrolyse the product failed, but further attempts to show the presence or absence of a nitrilic group, by chemical means, are in hand.

CHAPTER IV

Nucleophilic Substitutions in Heptachloroquinoline and Heptachloroisoquinoline:- The Use of ^{13}C N.M.R. in Assignment of Orientation

1. Substitution Reactions of Heptachloroquinoline and Heptachloroisoquinoline

1.1 Simple Nucleophiles

A. Introduction

(i) Reactions of Monohaloquinolines and Monohaloisoquinolines. Kinetic measurements on the displacement of bromine from all the monobromoquinolines, by alkoxide ion or amine, have shown that halogen atoms in the 2- and 4-positions react several orders of magnitude faster than halogens in other positions;[192] it can be considered that only halogen atoms in these positions undergo nucleophilic displacement under reasonably mild conditions.

The relative rates of reaction at the 2- and 4-positions of quinoline have been measured for a range of nucleophiles. For the reaction with ethoxide ion at 70°C, 2-chloroquinoline has a rate constant of $1{\cdot}9 \times 10^{-4}$ $l.mole^{-1}s^{-1}$, whereas the rate for 4-chloroquinoline is $1{\cdot}1 \times 10^{-4}$ $l.mole^{-1}$ s^{-1}.[193] In general, the reactivity of the 2- and 4-substituted compounds towards alkoxides is quite similar.

In contrast, amines normally react much more readily with 2-chloroquinoline than with 4-chloroquinoline, possibly because of greater steric crowding at the 4-position. The rate of reaction with amine at the 4-position is highly solvent dependent as shown in Table 4-1, which summarises rates of reactions of 2-chloroquinoline and 4-chloroquinoline with piperidine at 86·5°C, in various solvents.[194]

As far as isoquinoline is concerned, 1-chloroisoquinoline reacts with alkoxide ions at about the same rate as 2-chloroquinoline and 4-chloroquinoline,[193] but other monochloroisoquinolines react more slowly by several orders of magnitude, and might be considered to be unreactive towards nucleophilic attack.

TABLE 4-1

Reaction Rates of Monochloroquinolines with Piperidine

Solvent	Rate: $l.mole^{-1}s^{-1}$	
	2-Chloroquinoline	4-Chloroquinoline
Toluene	$0{\cdot}041 \times 10^{-4}$	unmeasurably small
Piperidine	$0{\cdot}310 \times 10^{-4}$	$0{\cdot}0091 \times 10^{-4}$
Methanol	$0{\cdot}258 \times 10^{-4}$	$0{\cdot}29 \times 10^{-4}$

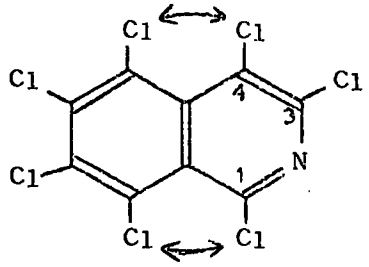
(ii) Factors Governing Orientation in Highly Chlorinated Heterocycles.

As seen in Chapter I, section 3.2.C, three main factors control the orientation of nucleophilic attack in perchlorinated heteroaromatic compounds, and these are the orientation of the ring nitrogen, the electronic effect of the chlorine atoms and steric effects.

Observations on monochloroquinolines indicate that, for heptachloroquinoline, the 2- and 4-positions are approximately equally activated by the ring nitrogen atom. Substitution in either of these positions has one chlorine atom ortho and one meta to the position of substitution, so the electronic effect of the chlorine atoms would not be expected to cause any distinction between the reactivity of the 2- and 4-positions. However, steric effects will quite probably make substitution at the 2-position considerably more favourable than substitution at the 4-position.

Observations on monochloroisoquinolines indicate that, for heptachloroisoquinoline, the 1-position is most activated by the ring nitrogen, so it might be expected that nucleophilic substitution of heptachloroisoquinoline would occur only at this position. However, it must be borne in mind that substitution in the 3-position is more favoured sterically, and by the electronic effect of the chlorine atoms, since there is an ortho and a meta chlorine atom, whereas at the 1-position there is only a meta and a para

chlorine atom.

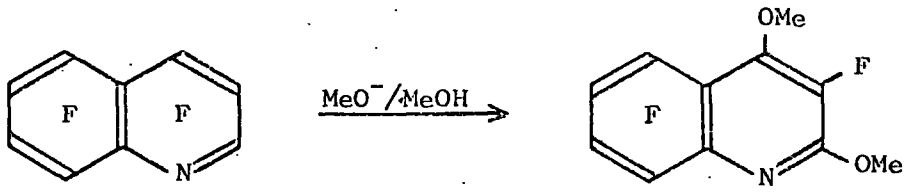


It is therefore possible that these two effects, between them, could outweigh the effect of the ring nitrogen atom and direct substitution of heptachloroisoquinoline to the 3-position.

(iii) Reaction of Heptafluoroquinoline and Heptafluoroisoquinoline.

It is worth considering the known orientations of substitution in these fluorinated compounds, because they may clarify some of the predictions made in section 1.1.A.(ii) for the corresponding chlorinated compounds.

Heptafluoroquinoline has only been found to undergo nucleophilic substitution in the 2- and 4-positions, and these positions are of comparable reactivity so that, when two equivalents of nucleophile such as methoxide are used, then pentafluoro-2,4-dimethoxyquinoline is produced.[195]



When one equivalent of nucleophile is used then generally a mixture of 2- and 4-substituted products is obtained, as summarised in Table 4-2. When steric crowding is reduced to a minimum (the reactions of ammonia) it can be seen that the reactivity of the 2- and 4-positions is very similar, but steric effects clearly favour the 2-position over the 4-position, as the size of the nucleophile is increased. These observations generally confirm the predictions made for heptachloroquinoline, but the large size of the chlorine atom compared to the fluorine atom would be expected to make

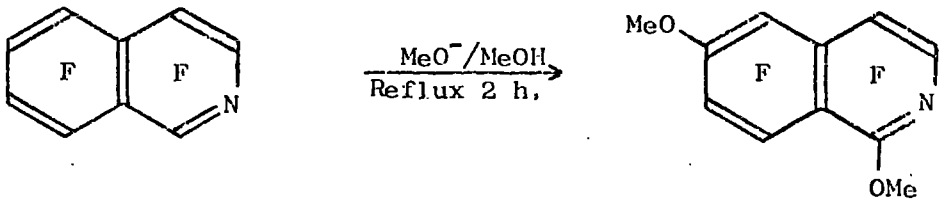
steric effects more important in heptachloroquinoline than in heptafluoroquinoline.

TABLE 4-2

Products of Nucleophilic Displacements in Heptafluoroquinoline

Nucleophile	Solvent	2-Isomer	4-Isomer	Reference
MeO^-	Methanol	75%	25%	195
MeO^-	t-Butanol	> 95%	-	196
NH_3	Acetone	50%	50%	195
NH_3	Ether	60%	40%	196
Et_2NH	Acetone	> 95%	-	196
n-BuLi	Hexane	> 95%	-	196
n-BuLi	Ether	90%	10%	196

Heptafluoroisoquinoline, with one equivalent of nucleophile, undergoes substitution exclusively at the 1-position,[195] as would be expected from the substitution rates of the monohaloisoquinolines, and the rate is comparable to that for heptafluoroquinoline. However, it is possible, under only moderately forcing conditions, to obtain disubstitution. For example, heptafluoroisoquinoline reacts with two equivalents methoxide ion to give pentafluoro-1,6-dimethoxyisoquinoline.[195]



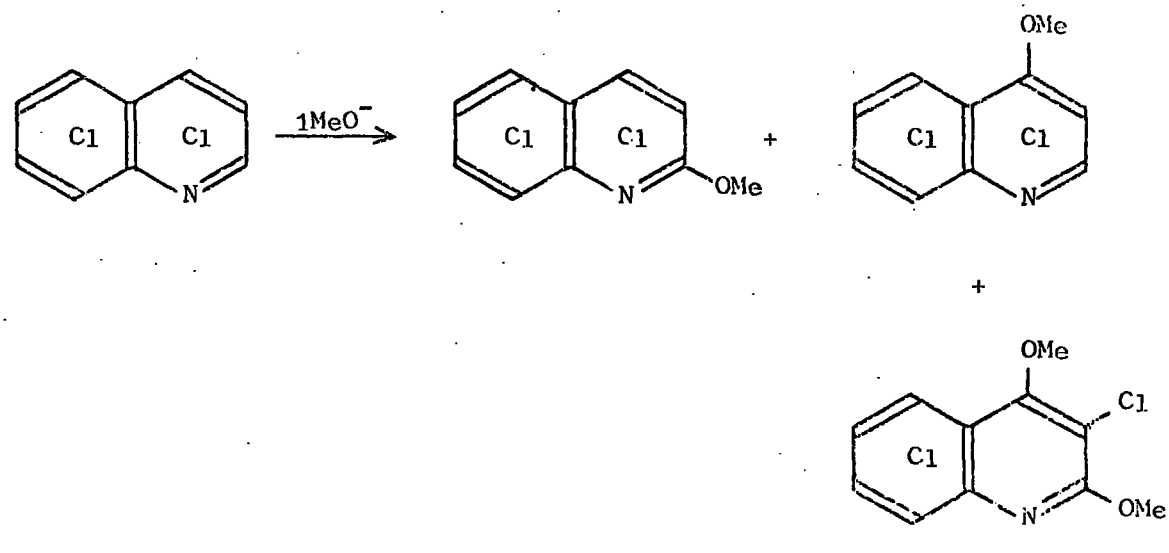
These observations tend to confirm the prediction that heptachloroisoquinoline will be reactive towards nucleophiles in the 1-position, but they suggest that it will not be reactive in the 3-position.

B. Displacements in Heptachloroquinoline and Heptachloroisoquinoline

(i) Heptachloroquinoline. Despite the fact that heptachloroquinoline is rather insoluble in most solvents, which means that most of these reactions were carried out on suspensions, it reacted with methoxide ion under conditions which are not much more forcing than those required for heptafluoroquinoline. This is in contrast to the low reactivity of hexachlorobenzene relative to hexafluorobenzene.[95]

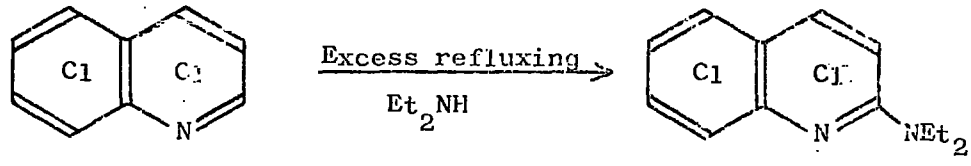
With one equivalent of methoxide ion, three products were produced: one is a pentachlorodimethoxyquinoline and the other two are hexachloro-methoxyquinolines. The relative amounts of the two monomethoxy compounds was at least 4:1 and only the major monomethoxy component could be isolated in a pure state. The same dimethoxy compound was obtained alone, by a reaction of heptachloroquinoline with two equivalents of methoxide ion.

Although there is no direct evidence, it is highly likely that the dimethoxy compound is pentachloro-2,4-dimethoxyquinoline, the major monomethoxy compound is hexachloro-2-methoxyquinoline, and the minor monomethoxy compound is hexachloro-4-methoxyquinoline.



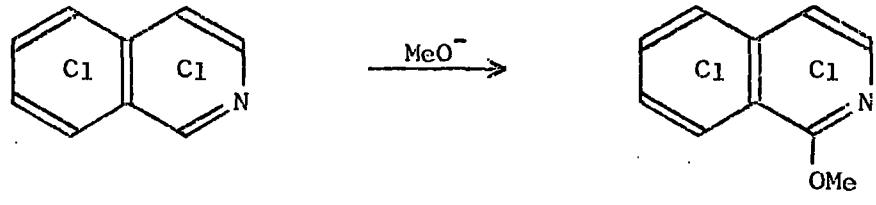
This is consistent with the predictions made at the beginning of this chapter; the size of the chlorine atoms causes even small nucleophiles to substitute much more readily at the 2-position than at the 4-position, although the electronic effect of the chlorine atoms is the same at both positions, because they both have one ortho and one meta chlorine atom.

With diethylamine, heptachloroquinoline readily gave a single monosubstituted quinoline, which is tentatively identified as hexachloro-2-diethylaminoquinoline, (see section 2.3.B, below). This too, is in accord with the 4-position becoming less reactive as the size of the nucleophile is increased, and there was no evidence for any disubstitution of heptachloroquinoline by diethylamine, even under quite forcing conditions.



(ii) Heptachloroisoquinoline. Like heptachloroquinoline, the insolubility of heptachlorisoquinoline caused the substitution reactions to be done on suspensions, but not much more vigorous conditions were needed than for heptafluoroisoquinoline.

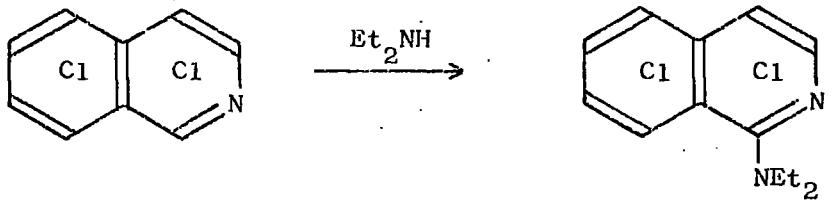
With one equivalent of methoxide ion, a single monosubstituted hexachloroisoquinoline was obtained, which is tentatively identified as hexachloro-1-methoxyisoquinoline, (see section 2.3.D, below).



Substitution occurs at the position which is most activated to nucleophilic attack by the ring system, and the directing effects of the chlorine atoms,

both electronic and steric, are obviously outweighed by the directing influence of the ring nitrogen atom.

Even when the steric effects were more severe, such as when diethylamine was the nucleophile, a single monosubstituted compound was obtained by reaction with heptachloroisoquinoline. There is no direct evidence, but this is probably hexachloro-1-diethylaminoisoquinoline.

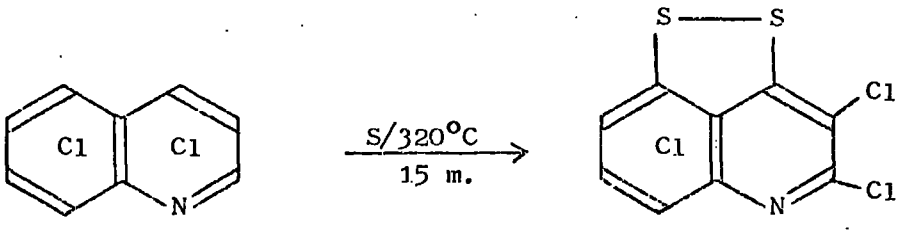


Unlike heptafluoroisoquinoline, it was not possible to obtain any disubstitution in heptachloroisoquinoline, even with methoxide ion under forcing conditions.

1.2 Sulphur Containing Nucleophiles

The treatment of heptachloroquinoline with sodium disulphide solution did not cause any reaction to occur, although this reagent does convert octachloronaphthalene to 2,3,4,5,6,7-hexachloronaphtho[1,8-cd]-1,2-dithiole.[101]

The more vigorous conditions, using elemental sulphur, which allow 3,4,7,8-tetrachloronaphtho[1,8-cd:4,5-c'd']bis[1 2]dithiole to be obtained from octachloronaphthalene,[101] were successful in converting heptachloroquinoline to 2,3,6,7,8-pentachloroquino[4,5-cd]-1,2-dithiole.

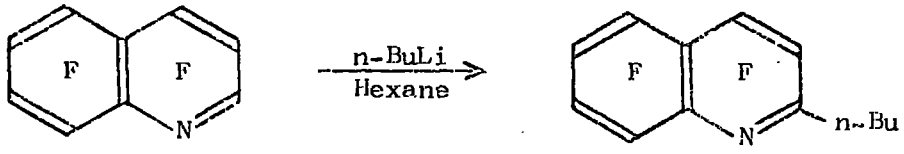


A pure sample of the product was obtained by recrystallisation and vacuum sublimation.

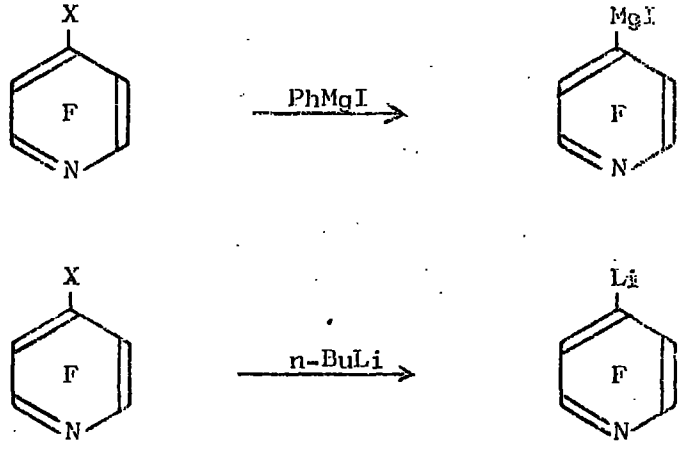
1.3 Organometallic Reagents

A. Introduction

As mentioned in Chapter I, perfluorinated heteroaromatic nitrogen compounds normally react with organometallic reagents to give alkyl substitution, and heptafluoroquinoline reacts with n-butyl lithium to give mainly 2-n-butylhexafluoroquinoline.[196]



Pentachloropyridine, however, undergoes metallation reactions and monohalotetrafluoropyridines also normally give metallation. For example, 4-bromotetrafluoropyridine and tetrafluoro-4-iodopyridine can produce Grignard reagents and lithio derivatives.[197,198]



However, attempts to make Grignard reagents or lithio derivatives of 2-bromohexafluoroquinoline and of 2,4-dibromopentafluoroquinoline have only led to extensive decomposition.[199]

B. Reaction of Heptachlorquinoline with n-Butyl Lithium

When heptachloroquinoline was treated with n-butyl lithium and then the reaction mixture hydrolysed, only dark tarry materials, resulting from extensive decomposition, were obtained; this was so, even when the whole reaction was carried out at -78°C.

This result, together with the earlier results on bromofluoroquinolines, suggests that some feature of the quinoline ring system, which is different to the pyridine ring system, makes its organometallic derivatives very unstable. While it is easy to envisage several ways in which such derivatives could decompose, it is not clear why they should be so much less stable than the corresponding derivatives of pyridine.

2. ^{13}C N.M.R. and its Attempted Use in Assigning Orientation of Substitution

Textbooks on ^{13}C nuclear magnetic resonance spectroscopy have recently been published. There is a general introduction to its application in organic chemistry,[200] as well as tables of observed spectra,[201] but it is only within the last ten years that this form of spectroscopy has become at all widely used.

2.1 General Principles of ^{13}C N.M.R.

A. Nuclear Sensitivity and Natural Abundance

Carbon-13 is the only stable isotope of carbon to have a nuclear spin, and its spin number is $\frac{1}{2}$; in this respect, nuclear resonance spectroscopy of carbon-13 is similar to spectroscopy of the proton. However, there are some important differences between carbon-13 and the proton.

First, the magnetogyric ratio for carbon-13 is only about $\frac{1}{4}$ that of the value for a proton; accurate measurements give the ratio to be 0·251443.[202,203] Now the energy difference, ΔE, between the two magnetic energy levels of a nucleus is given by

$$\Delta E = \gamma h H$$

where γ is the magnetogyric ratio, h is Planck's constant and H is the applied magnetic field. Hence, for a given magnetic field, the energy difference between the two levels will be less for a carbon-13 nucleus than for a proton, and, by the Boltzmann energy distribution, the excess population of the ground state, relative to the excited state, will be less.

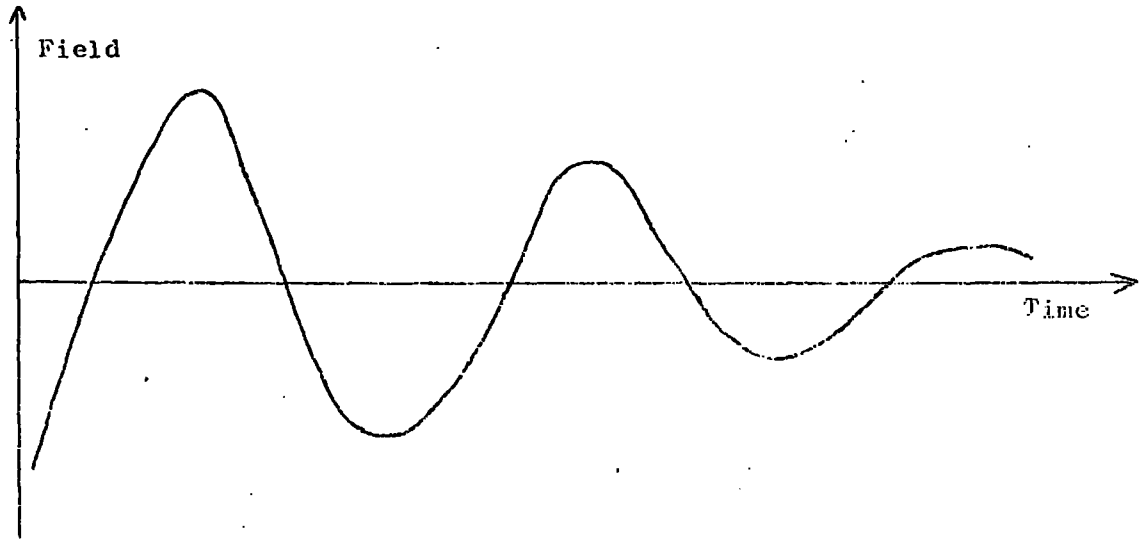
This means that the carbon-13 nucleus is intrinsically less sensitive than a proton by a factor of about 64.

Secondly, spectroscopic measurements are normally made on samples containing only the natural abundance of carbon-13, which is about 1·1%. Obviously, this further lowers the sensitivity compared to proton spectroscopy, and overall the technique is less sensitive by a factor of about 6000.

B. The Use of Pulsed Fourier Transform

Pulsed Fourier transform techniques can be used for all forms of nuclear resonance spectroscopy, but they are particularly useful in combating the low sensitivities encountered with carbon-13 n.m.r. A conventional n.m.r. spectrometer irradiates the sample with a continuous radio-frequency wave and records absorbtions from this wave as a function of frequency; only one type of carbon environment is excited, and hence observed, at any given time.

However, if the sample is irradiated with a short, high power, radio-frequency pulse, then it is possible to excite all the carbon nuclei, in their various environments, at once. The emissions of radio-frequency waves, as the system relaxes, may then be observed. If there is only one type of nucleus in the sample, then this emission will be of a single frequency, with the intensity falling with time, as shown.



In practice, where there are several types of nuclei, several different, but similar, emission frequencies are observed and beat patterns are produced. The mathemtaical operation of Fourier transformation, for which computer facilities are required and which isolates the component frequencies from a complex wave form, allows these results to be presented in the more familiar curve of absorbtion against frequency.

This technique is pulsed Fourier transform spectroscopy; its value lies in the fact that it takes less time to record the whole spectrum once by this technique, than it does by the continuous wave method. The spectrum is normally recorded many times and summed to improve the signal to noise ratio. Fourier transform allows as good a signal to noise ratio to be achieved in less time than is required in a continuous wave experiment, or if the same time is spent on recording the same spectrum by the two methods, then the signal to noise ratio for the Fourier transform spectrum will be greater by a factor of about 10.

C. The Nuclear Overhauser Effect and Spin-Spin Coupling

As mentioned in section 2.1.A, the excess of population in the ground state, relative to the excited state, is very small for carbon-13 nuclei, and methods of relaxation from the excited state are important, to prevent the sample from becoming rapidly saturated. An important relaxation method is through interaction between the dipole of the carbon-13 nucleus and the dipoles of adjacent nuclei; interaction with protons is most important. When a ^{13}C n.m.r. experiment is being carried out, it is usual to excite all the protons by a broad band radio-frequency field, for two main reasons.

First, the disturbance of the protons increases the efficiency of the dipolar relaxation of carbon-13 and leads to a signal enhancement, known as the Nuclear Overhauser Effect. The increased relaxation efficiency can be pictured as arising from the tendency for carbon-13 nuclei and protons to be

spin paired. The signal enhancement is greatest as the number of protons directly bonded to a carbon atom increases, and this effect means that the integration of peak areas in a ^{13}C n.m.r. spectrum does not provide very meaningful information on the relative numbers of different types of carbon atoms present.

Secondly, all spin-spin coupling between ^{13}C and ^{1}H is destroyed and the ^{13}C spectrum is greatly simplified. Normally, ^{13}C spectra show no coupling between two or more carbon-13 nuclei either, because of the low natural abundance, which makes it unlikely that two carbon-13 nuclei will be present in one molecule and able to couple. The only spin-spin coupling which is normally seen is that between carbon-13 and other spin $\frac{1}{2}$ nuclei, such as fluorine-19.

D. Features of Chemical Shifts

In a proton n.m.r. spectrum, it is usual to obtain structural information from the chemical shifts, peak areas and spin-spin coupling. As mentioned in section 2.1.C, peak areas and spin-spin coupling are not very useful in carbon-13 observations and much greater emphasis is placed on chemical shift measurements.

These cover a much wider range than do proton shifts (about 200 p.p.m. for organic compounds) are are normally measured relative to the same standard, tetramethylsilane. Most shifts are downfield from T.M.S. and downfield shifts are quoted as positive, which is the same convention as that usually used for protons, but the opposite convention to that usually used for fluorine-19 nuclei. Generally, carbon atoms which absorb at low field in the ^{13}C spectrum, carry protons which also absorb at low field in the ^{1}H spectrum, so that aromatic carbons are further downfield than olefinic carbons, which are further downfield than paraffinic carbons.

2.2 Earlier ^{13}C N.M.R. Observations on Chloroaromatic Compounds

There has been very little work reported on highly chlorinated compounds, because of the difficulties of assigning absorbtions to particular carbon atoms when there is no spin-spin coupling. It is, however, possible to assign the peaks of hydrogenated compounds by only partially removing the spin-spin coupling and recently spectra of perchlorocarbons have been assigned from the couplings in their monohydro analogues.[204]

A. Chlorobenzenes and Substituent Chemical Shifts

Benzene itself has, of course, only one type of carbon atom in the n.m.r. spectrum,[205] but chlorobenzene has four types. These may be assigned from the partial coupling to hydrogen, and the changes in chemical shift of the various carbon atoms in the ring caused by the replacement of C-H by C-Cl can then be calculated.[205] These changes are known as substituent chemical shifts and their values are:

Carbon Atom	Shift p.p.m.
Carbon Substituted	+5·63
Carbon Ortho	+0·05
Carbon Meta	+1·43
Carbon Para	-1·86

Positive values indicate that, according to the convention used here, absorbtions are at lower field than in the unsubstituted compound.

Using the known chemical shift for benzene and these substituent chemical shifts for the replacement of C-H by C-Cl, the spectra of ortho dichlorobenzene and meta dichlorobenzene have been calculated and compared with the observed spectra.[205] Generally the agreement is quite good, to within less than 1 p.p.m.

B. Chloropyridines and Chlorodiazines

The ^{13}C n.m.r. spectra of pyridine, pyridazine, pyrimidine and pyrazine, have all been measured and assigned by the partial couplings to hydrogen nuclei.[206] Although the substituent chemical shifts for the replacement of C-H by C-Cl given in section 2.2.A, were for carbocyclic aromatic compounds, they have been applied to predict the spectra of pentachloropyridine and all the tetrachlorodiazines,[207] using the assigned spectra of the parent hydrogen compounds. When these predicted spectra are compared with the observed spectra,[207] which cannot be directly assigned, the agreement is sufficient to allow full assignments of the observed spectra to be made.

2.3 Work on Chloroquinolines and Chloroisoquinolines

A. Heptachloroquinoline

The ^{13}C n.m.r. spectrum of quinoline has been measured and completely assigned, using partial spin-spin couplings.[208] Using this spectrum, and the substituent chemical shifts for the replacement of C-H by C-Cl measured from benzene derivatives,[205] it is possible to predict the ^{13}C n.m.r. spectrum of heptachloroquinoline. This predicted spectrum is compared with the observed spectrum in Table 4-3. The peaks are arranged in order of increasing chemical shift downfield from T.M.S. (but taken as positive), and the integration of the observed spectrum is expected to be more accurate than is normally the case in ^{13}C n.m.r., because there are no hydrogen atoms in the molecule.

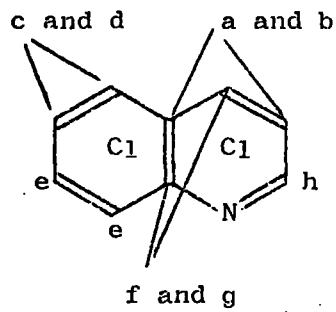
As there are only eight peaks in the observed spectrum, one of these must correspond to two carbon atoms which have almost identical chemical shifts and, from the integration, it is clear tha peak e must be the one which corresponds to two carbon atoms. Although the correlation between the predicted and observed spectra is not very good, it is possible to make some

TABLE 4.3

Calculated and Observed ^{13}C N.M.R. Chemical Shifts for Heptachloroquinoline

Calculated		Observed		
Ring Position	Shift p.p.m.	Peak	Shift p.p.m.	Integration
3	126·5	a	123·4	27
10	127·3	b	127·8	22
5	132·9	c	131·5	19
6	133·4	d	132·7	19
8	134·5	e	135·5	61
7	136·3			
4	142·8	f	141·2	20
9	147·4	g	141·5	18
2	157·1	h	150·6	14

assignments of the observed spectrum from this table. For example, peak h is the only one with anything like as great a chemical shift as that predicted for the 2-carbon atom, so peak h may be assigned as being due to that carbon atom. The fullest assignment which can be made with reasonable certainty is shown below.



B. Hexachlorodiethylaminoquinoline

The observed ^{13}C n.m.r. spectrum of the monosubstituted compound obtained by reacting heptachloroquinoline with diethylamine is given in

Appendix 3. The carbon atoms of the ethyl groups would be expected to absorb at a completely different chemical shift position from that of the aromatic ring carbons, and are the two peaks at 13·0 p.p.m. (corresponding to the methyl groups) and at 44·8 p.p.m. (corresponding to the methylene groups).

Observations on aminochloropyridines have allowed substituent chemical shifts for the replacement of C-Cl by C-NR_2 in highly chlorinated aromatic systems to be measured, and the values obtained are:[207]

Carbon Atom	Shift p.p.m.
Carbon Substituted	+ 8·4
Carbon Ortho	-12·8
Carbon Meta	- 2·6
Carbon Para	~ -11

Using these shift values, and the partially assigned spectrum of heptachloroquinoline, the predicted spectra of the various hexachlorodiethylaminoquinolines may be calculated, as is done in Table 4-4, which also gives the observed spectrum of the ring carbon atoms.

As can be seen, the observed spectrum has a peak with a greater downfield shift than heptachloroquinoline itself, and this is only true of the predicted spectrum for the 2-diethylamino compound. The ^{13}C n.m.r. evidence therefore tends to identify this compound as hexachloro-2-diethylaminoquinoline. The correlation between the observed and predicted spectra is not very good and this limits the extent to which the observed spectrum can be assigned. This poor correlation is partly due to the fact that the spectrum of heptachloroquinoline itself is not completely assigned, but it also suggests that substituent chemical shifts for the replacement of C-Cl by C-NR_2 vary quite considerably between highly

chlorinated pyridines and highly chlorinated quinolines.

TABLE 4-4

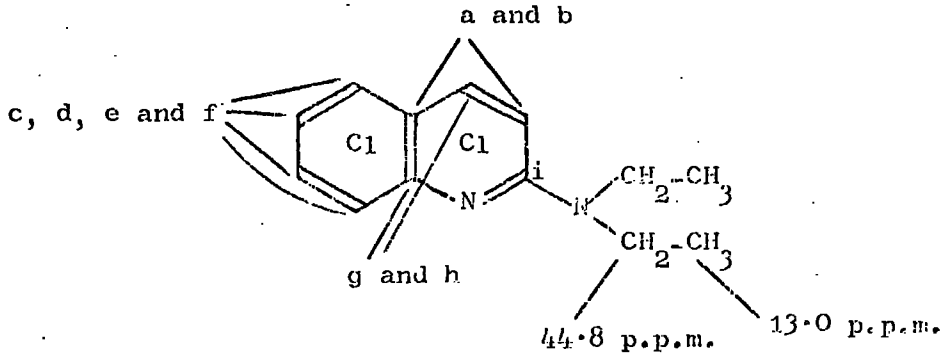
Calculated ^{13}C N.M.R. Chemical Shifts for Various Diethylamino Hexachloroquinolines

Ring Carbon Atom \ Position of Diethylamino Substituent	2	3	4	5	6	7	8
2	159	138	148	150·6	150·6	150·6	150·6
3	113	133	112	125	125	125	125
4	138	127	149	141	141	141	141
5	132	132	132	140	119	129	121
6	132	132	132	119	140	119	129
7	135·5	135·5	135·5	133	124	144	123
8	135·5	135·5	135·5	124	133	124	144
9	138	130	138	138	130	138	130
10	114	122	112	112	122	114	122

Observed Spectrum

Peak	a	b	c	d	e	f	g	h	i
Shift p.p.m.	119·5	121·9	127·3	128·9	130·3	133·5	139·6	141·3	155·1

The assignment of the observed spectrum of hexachloro-2-diethylamino-quinoline can thus only be very partial, and the figure below shows all that can be stated with reasonable certainty.



C. Heptachloroisoquinoline

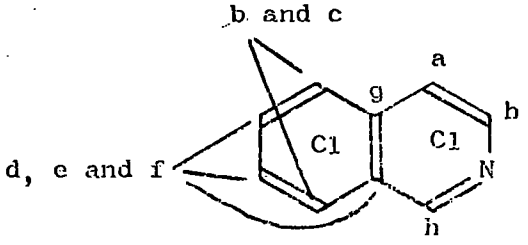
As in the case of heptachloroquinoline, a prediction of the spectrum of heptachloroisoquinoline may be made from the assigned spectrum of isoquinoline,[208] and substituent chemical shifts for the replacement of C-H by C-Cl. This predicted spectrum is compared with the observed spectrum in Table 4-5.

TABLE 4-5

Calculated and Observed ^{13}C N.M.R. Chemical Shifts for Heptachloroisoquinoline

Calculated		Observed		
Ring Position	Shift p.p.m.	Peak	Shift p.p.m.	Integration
4	124·0	a	123·5	76
5	131·5	b	124·5	89
8	132·6	c	128·7	91
7	134·2	d	130·1	89
9	134·8	e	134·9	98
6	137·3	f	135·8	88
10	145·1	g	139·7	65
3	146·5	h	146·2	220
1	157·7			

As with heptachloroquinoline, one of the observed peaks must account for two ring carbon atoms, and integration clearly shows that this must be peak h. A tentative partial assignment of the observed spectrum can be made as shown below.



The limitations of this method of calculating a predicted spectrum are illustrated by the difference of 11·5 p.p.m. between the true shift of the 1-carbon atom, and its calculated value.

D. Hexachloromethoxyisoquinoline

It is unfortunate that ^{13}C n.m.r. spectra have only been measured on a diethylamino substituted quinoline, and a methoxy substituted isoquinoline, but this was because of the difficulty of preparing or purifying sufficient amounts of other derivatives.

The observed ^{13}C n.m.r. spectrum of the monosubstituted compound, obtained by reacting heptachloroisoquinoline with one equivalent of methoxide ion, is given in Appendix 3. Clearly, the peak at 54·7 p.p.m. corresponds to the carbon atom of the methoxy group, and the other peaks are due to the ring carbon atoms.

Observations on methoxychloropyridines have allowed substituent chemical shifts for the replacement of C-Cl by C-OCH_3 in highly chlorinated aromatic systems to be measured, and the values obtained[207] are:

Carbon Atom	Shift p.p.m.
Carbon Substituted	+23·8
Carbon Ortho	-14·9
Carbon Meta	- 0·1
Carbon Para	- 6·1

Using these shift values, and the partially assigned spectrum of heptachloroisoquinoline, the predicted spectra of the various hexachloromethoxyisoquinolines may be calculated, as is done in Table 4-6, which also gives the observed spectrum of the ring carbon atoms.

When compared with the observed spectrum, none of these predicted spectra correlates very well, but there are two features of the predicted

TABLE 4-6

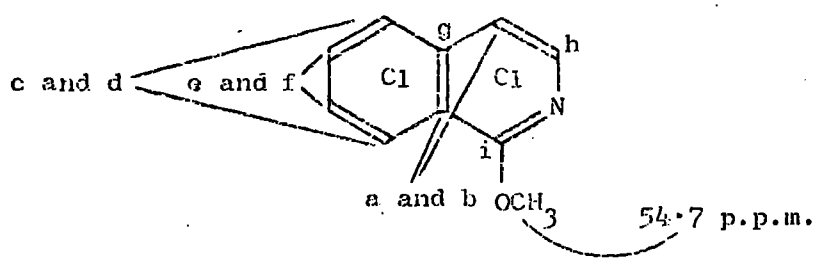
Calculated ^{13}C N.M.R. Chemical Shifts for Various Methoxy Hexachloroisoquinolines

Ring Carbon Atom \ Position of Methoxy Substituent	1	3	4	5	6	7	8
1	170·0	146·1	140·1	146·2	146·2	146·2	146·2
3	146·1	170·0	131·3	146·2	146·2	146·2	146·2
4	117·4	108·6	147·3	123·5	123·5	123·5	123·5
5	125	125	125	149	110	125	119
6	132	132	132	117	156	117	132
7	132	132	132	132	117	156	117
8	125	125	125	119	125	110	149
9	117·1	127·9	132	132	126	132	117
10	139·6	139·6	124·8	125	139·6	133·6	139·6

Observed Spectrum

Peak	a	b	c	d	e	f	g	h	i
Shift p.p.m.	113·0	114·7	125·2	127·3	130·4	131·2	135·6	142·5	153·1

spectrum for the 1-substituted compound which make it correlate better than any of the others. First, there is a peak in the observed spectrum at a significantly greater shift than any peak in heptachloroisoquinoline itself, and secondly there are two peaks between 110 and 120 p.p.m. Only the predicted spectrum for 1-substitution has both these features, so the compound may be tentatively identified as hexachloro-1-methoxyisoquinoline. The partially assigned spectrum would then be as shown below:



E. General Conclusions

^{13}C n.m.r. spectra of chlorinated quinolines and isoquinolines have allowed some tentative assignments of structure to be made, but all correlations between predicted and observed spectra are rather poor, and the highly tenuous nature of the assignments makes it unlikely that ^{13}C n.m.r. will be a very valuable tool for structural measurements in perchloro-aromatic compounds. It is desirable that spectra of a wider range of materials should be obtained, and that an improved method for calculating predicted spectra should be devised.

2.4 Connection with Octachloronaphthalene

A. Work on Hexachlorobenzene and Pentachloropyridine

The method of predicting spectra of highly chlorinated heterocycles from the known spectrum of the parent heterocycle, and from substituent chemical shifts for the replacement of C-H by C-Cl, has been seen to have several difficulties.

An alternative approach is to compare the known and assigned spectra of hexachlorobenzene and pentachloropyridine, and so calculate substituent chemical shifts for the replacement of C-Cl by N, in highly chlorinated aromatic systems, and these shifts are given below.[207]

Carbon Atom	Shift p.p.m.
Carbon Ortho	12·9
Carbon Meta	- 4·0
Carbon Para	11·0

When these values, and the known spectrum of hexachlorobenzene, are used to calculate the spectra of the tetrachlorodiazines, the predicted spectra generally agree with the observed spectra rather better than do spectra predicted by the other method.

It may be that comparison of octachloronaphthalene with heptachloroquinoline and heptachloroisoquinoline, will allow fuller assignments of the spectra of substituted chloroquinolines and chloroisoquinolines to be made.

B. Comparison between Octachloronaphthalene and Heptachloroquinoline

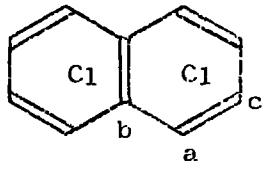
The observed ^{13}C n.m.r. spectrum of octachloronaphthalene is given in Table 4-7.

TABLE 4-7

Observed ^{13}C N.M.R. Chemical Shifts for Octachloronaphthalene

Peak	Shift p.p.m.	Integration
a	128·9	59
b	129·6	24
c	135·2	97

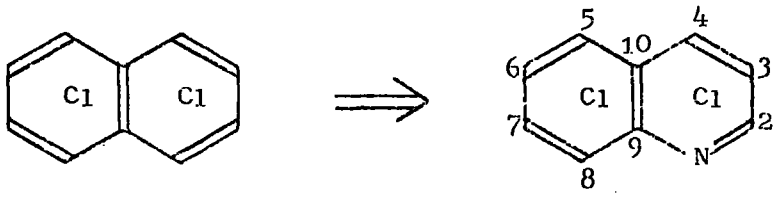
Peak b can clearly be assigned to the 9 and 10 carbon atoms because of its lower integration, but a means of assigning the other two peaks is not immediately obvious. However, there are only two possible alternatives and, taking each in turn and using the substituent chemical shifts for the replacement of C-Cl by N given in section 2.4.A, two predictions of the spectrum of heptachloroquinoline may be made. Only when peak a corresponds to the 1-carbon atom is a reasonable chemical shift for the 2-carbon atom of heptachloroquinoline obtained, so the spectrum of octachloronaphthalene may be completely assigned as shown below:



Since the spectrum of heptachloroquinoline has already been partially assigned, and the shift position of each carbon atom is known to within about 1 p.p.m., it is possible to calculate substituent chemical shifts for the replacement of C-Cl in octachloronaphthalene by N, to give heptachloroquinoline, and the results are given in Table 4-8.

TABLE 4-8

Substituent Chemical Shifts for the Replacement of C-Cl by N to Give Heptachloroquinoline



Carbon Atom	Shift p.p.m.
2	+15·4
3	-11
4	+12
5	+ 3
6	- 3
7	+ 0·3
8	- 6·6
9	-12
10	+ 5

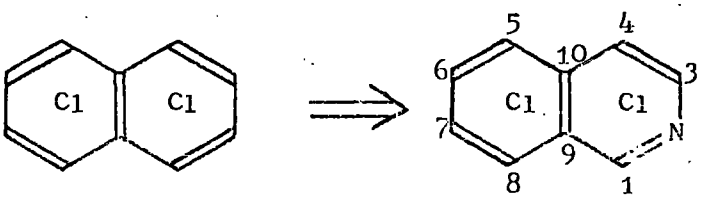
It is noticeable that there is quite a large difference between these values and those for the replacement of C-Cl by N, obtained by comparing hexachlorobenzene and pentachloropyridine.

C. Comparison between Octachloronaphthalene and Heptachloroisoquinoline

If the fully assigned spectrum of octachloronaphthalene is similarly compared with the partially assigned spectrum of heptachloroisoquinoline, the shifts for the replacement of C-Cl in octachloronaphthalene by N, to give heptachloroisoquinoline, may be calculated, and the results are given in Table 4-9.

TABLE 4-9

Substituent Chemical Shifts for the Replacement of C-Cl by N to Give Heptachloroisoquinoline



Carbon Atom	Shift p.p.m.
1	+17·3
3	+11·0
4	- 5·4
5	- 3
6	- 2
7	- 2
8	- 3
9	+ 4
10	+10·1

Again these values differ quite considerably from those for the replacement of C-Cl by N, obtained by comparing hexachlorobenzene with pentachloropyridine, or by comparing octachloronaphthalene with heptachloroquinoline.

D. Substituted Chlorinated Quinolines and Isoquinolines

It is likely that the substituent chemical shifts for the replacement of C-Cl by N, given in Tables 4-8 and 4-9, will not vary much if one or two chlorine atoms are replaced by some other group. Hence, if monosubstituted or disubstituted octachloronaphthalenes could be prepared and their spectra assigned, quite accurate predictions of the spectra of the corresponding substituted quinolines and isoquinolines could probably be made. This should be an aid in assigning the spectra of substituted heptachloroquinolines and heptachloroisoquinolines, so it is desirable to carry out some substitution reactions on octachloronaphthalene.

3. Substitution Reactions of Octachloronaphthalene

Klingsberg has remarked that no simple nucleophilic substitution reactions of octachloronaphthalene have been reported,[101] and it may be that this is because octachloronaphthalene is rather inert, like hexachlorobenzene.

3.1 Reaction with Methoxide Ion

Octachloronaphthalene was completely unaffected by methoxide ion in methanol, even when the conditions were made as vigorous as possible, by using high temperatures, high pressures, and long reaction times.

3.2 Reaction with Amines

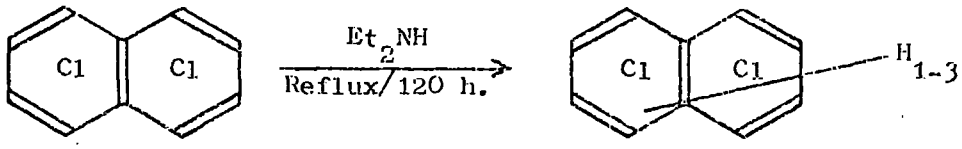
A. Reaction with Diethylamine in Sulpholane

Octachloronaphthalene was also completely unaffected by diethylamine in sulpholane as solvent and using fairly forcing conditions.

B. Reaction with Excess Diethylamine

When octachloronaphthalene was refluxed for a prolonged period with excess diethylamine to try and persuade nucleophilic substitution to occur, reductive dechlorination occurred instead, and a mixture of non-fully

chlorinated naphthalenes was obtained.



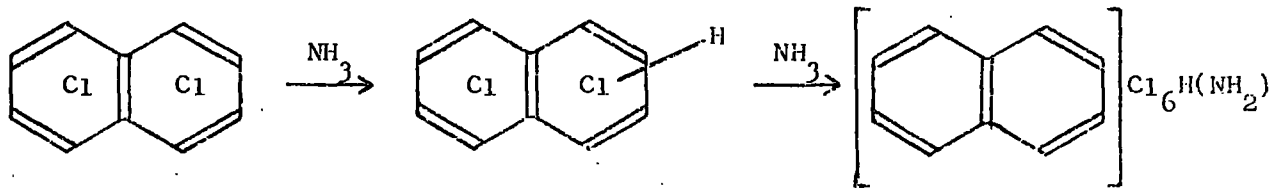
This is another example of reductive dechlorination competing successfully with substitution, presumably by the mechanism described earlier, involving electron transfer to the aromatic system.

C. Reaction with t-Butylamine

t-Butylamine is a very sterically hindered molecule so it would be expected, like diethylamine, to give reductive dechlorination, and reaction is quite likely to be rather slow. This is indeed so, for, when octachloronaphthalene was reacted with t-butylamine under fairly forcing conditions, a lot of starting material was recovered, as well as some heptachloronaphthalene.

D. Reaction with Ammonia

As ammonia is the smallest molecule which may be classed as an amine, it is the amine most likely to give a substitution reaction with octachloronaphthalene. In practice, when octachloronaphthalene was reacted with excess ammonia a mixture of heptachloronaphthalene and aminohexachloronaphthalene was obtained, indicating that reductive dechlorination occurs first and that the product undergoes a nucleophilic substitution reaction.



The aminohexachloronaphthalene was the main component of the mixture and it was isolated, but the orientation of the various groups is not known.

3.3 Reaction with Lithium Diethylamide

As the diethylamide anion is such a powerful nucleophile, it should be more likely to effect substitution of octachloronaphthalene than almost anything else. However, when octachloronaphthalene was reacted with lithium diethylamide, a lot of decomposition occurred and the only identifiable material obtained was unchanged octachloronaphthalene, in very low recovery.

3.4 Conclusion

It has not so far been possible to prepare any simple substituted octachloronaphthalenes for ^{13}C n.m.r. measurements. It has therefore not been possible to use such compounds to help make assignments of the spectra of chlorinated quinolines and isoquinolines.

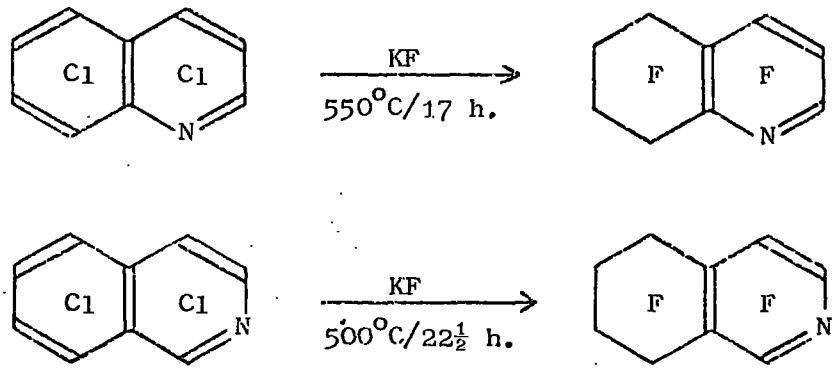
CHAPTER V

Perfluoro-5,6,7,8-tetrahydroquinoline and -isoquinoline:- The Mechanism of Their Formation and Some of Their Properties

1. Introduction

1.1 Preparation of Perfluoro-5,6,7,8-tetrahydroquinoline and -isoquinoline

The reactions of heptachloroquinoline[209] and heptachloroisoquinoline[210] with potassium fluoride in an autoclave, which are the standard syntheses of heptafluoroquinoline and heptafluoroisoquinoline, also produce small amounts of more volatile products. In each case, the amount of more volatile products may be increased by raising the temperature, and these products may be isolated and shown to be perfluoro-5,6,7,8-tetrahydroquinoline and perfluoro-5,6,7,8-tetrahydroisoquinoline.



Perfluoro-5,6,7,8-tetrahydroisoquinoline has also been prepared by fluorination of heptafluoroisoquinoline with cobalt trifluoride,[210] or by reaction of tetrafluoro-4-nitropyridine with tetrafluoroethylene.[211]

1.2 Earlier Work on Possible Mechanisms of Their Formation

The formation of perfluoro-5,6,7,8-tetrahydroquinoline, during the autoclave fluorination of heptachloroquinoline, has been quite extensively investigated,[209] and similar results probably apply to the analogous isoquinoline reaction. The mechanism tentatively proposed involves the

initial fluorination of heptachloroquinoline to heptafluoroquinoline, which can then react with chlorine which is present in small amounts because of thermal decomposition of chlcrinated compounds. The chlorine adds to the carbocyclic ring, giving a material which may either dechlorinate back to heptafluoroquinoline, or halogen exchange. Chlorination followed by halogen exchange would form the perfluoro-5,6,7,8-tetrahydroquinoline which is observed experimentally. The overall reaction scheme is as shown in Figure 5-1, and the evidence in support of this mechanism may be summarised as:

(i) Autoclave fluorinations of chlorinated compounds produce considerable amount of chlorine.

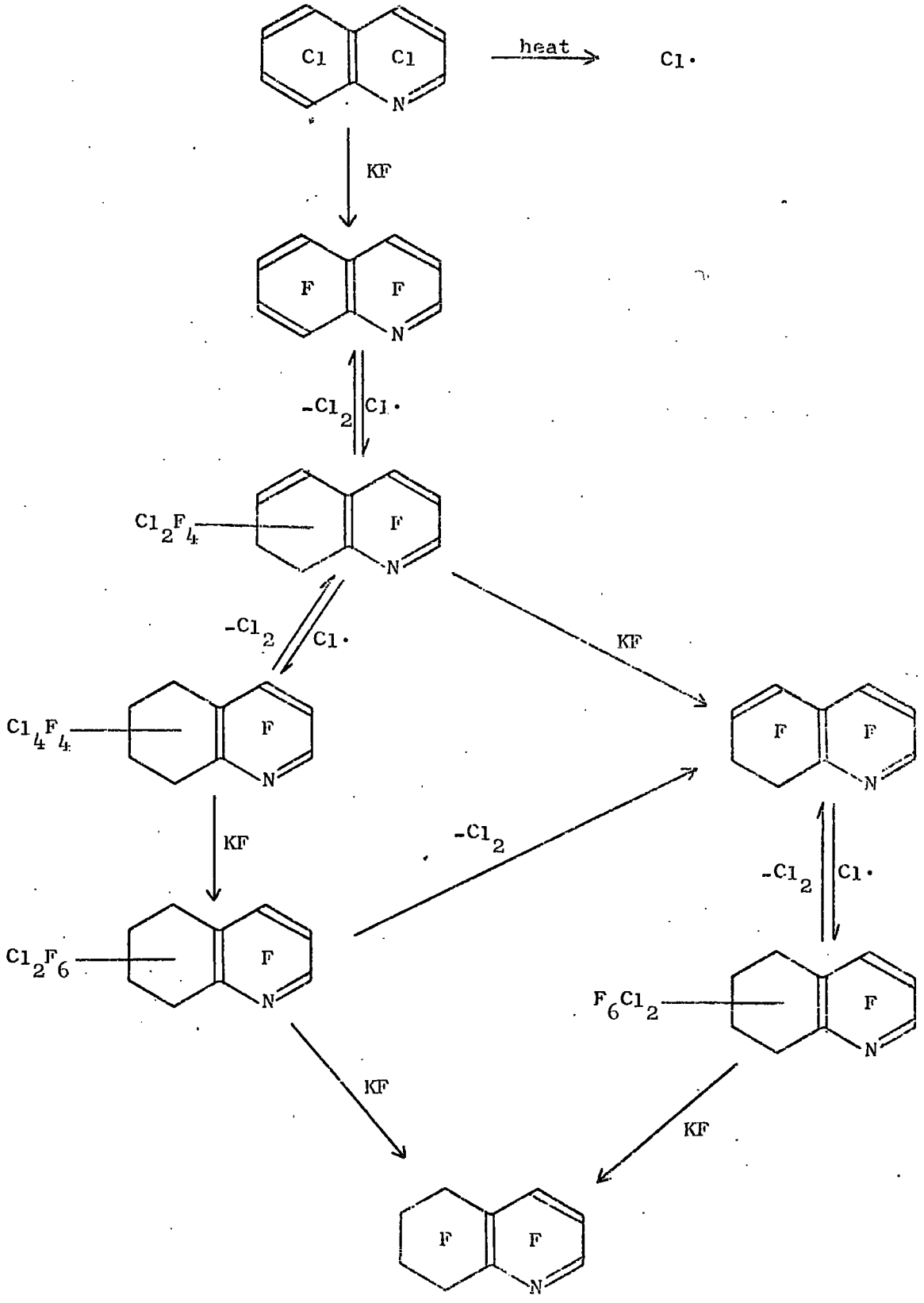
(ii) When chlorine is reacted with heptachloroquinoline, in the presence of potassium fluoride, no volatile products are obtained.

(iii) Chlorine reacts readily with heptafluoroquinoline in a light-induced radical process, to give 5,6,7,8-tetrachloroheptafluoroquinoline.

(iv) Reaction of 5,6,7,8-tetrachloroheptafluoroquinoline with potassium fluoride in an autoclave under particular conditions gives almost the same product mixture as from the reaction of heptachloroquinoline with potassium fluoride under the same conditions.

It has been suggested[209] that if 5,6,7,8-tetrachloroheptafluoroquinoline could be converted to perfluoro-5,6,7,8-tetrahydroquinoline by halogen exchange in a solvent, this would provide additional evidence for this mechanism. If the formation of perfluoro-5,6,7,8-tetrahydroisoquinoline in an autoclave involves the same mechanism, then it should be possible to prepare 5,6,7,8-tetrachloroheptafluoroisoquinoline and convert this to perfluoro-5,6,7,8-tetrahydroisoquinoline by halogen exchange in a solvent.

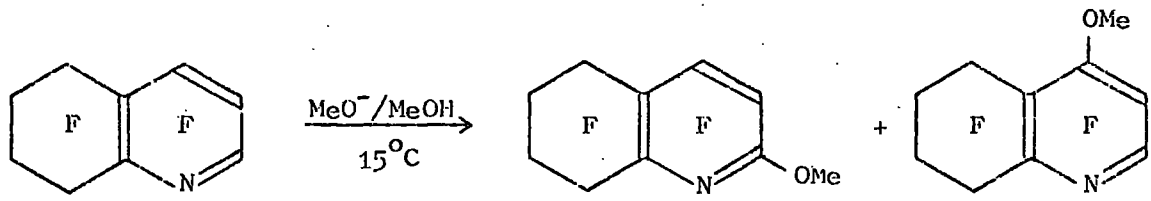
FIGURE 5-1


Cl
Cl
N
heat
Cl·
KF
F
F
N
-Cl2
Cl·
Cl2F4
F
N
-Cl2
Cl·
KF
Cl4F4
F
N
F
F
N
KF
-Cl2
-Cl2
Cl·
Cl2F6
F
N
F6Cl2
F
N
KF
KF
F
F
N

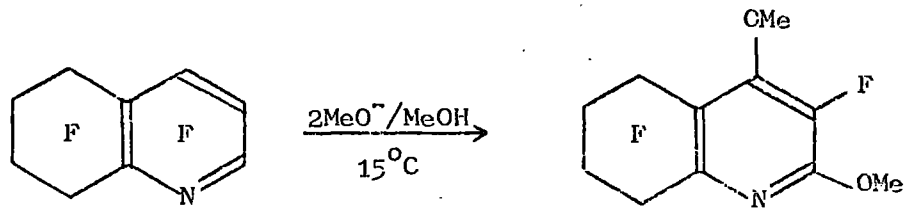
1.3 Earlier Work on Reactions of Perfluoro-5,6,7,8-tetrahydroquinoline

Nucleophilic substitution is the reaction which has been most studied, and this is of some theoretical interest because the substrate may be regarded as a dialkyl pyridine, and the orientation of substitution might be influenced by this.

It has been found,[212] that the 2- and 4-positions are of similar reactivity for, when reacted with one equivalent of methoxide ion, both 2- and 4-substituted systems are obtained.



A similar reaction has been obtained with ammonia and, with methoxide ion, disubstitution is readily achieved.

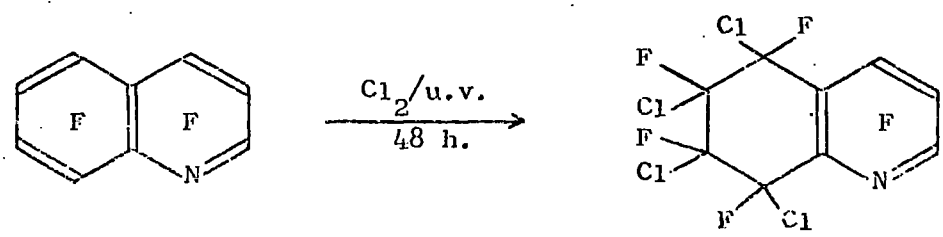


2. Mechanistic Investigations

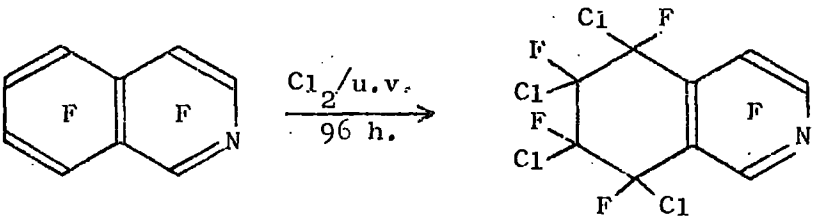
2.1 Fluorinations of 5,6,7,8-Tetrachloroheptafluoroquinoline and -isoquinoline

A. Preparation of Starting Materials

(i) 5,6,7,8-Tetrachloroheptafluoroquinoline. This was prepared by the method used earlier,[213] which was the reaction between chlorine gas and heptafluoroquinoline, under the influence of ultra-violet light.



(ii) 5,6,7,8-Tetrachloroheptafluoroisoquinoline. Reaction between chlorine gas and heptafluoroisoquinoline, under the same conditions as those used for the preparation of 5,6,7,8-tetrachloroheptafluoroquinoline, gave only partial reaction, and a lot of starting material was recovered. However, it was possible to obtain pure 5,6,7,8-tetrachloroheptafluoroisoquinoline by more prolonged irradiation, followed by vacuum transfer.



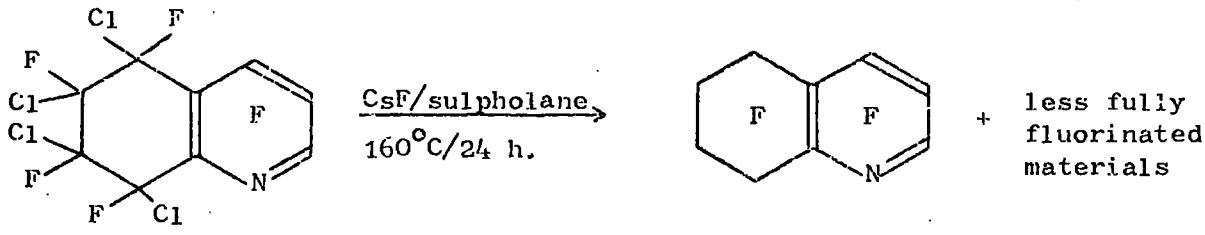
It is not at all clear why the carbocyclic ring of isoquinoline should be less susceptible to radical addition than the carbocyclic ring of quinoline.

B. Fluorination at Atmospheric Pressure

(i) 5,6,7,8-Tetrachloroheptafluoroquinoline. Dry caesium fluoride was used as the reagent, since the reaction was only carried out on a small scale and this is the most active reagent available. Initially sulpholane was used as the solvent, but this was not a successful method because the product and solvent had similar volatilities and separation was very difficult.

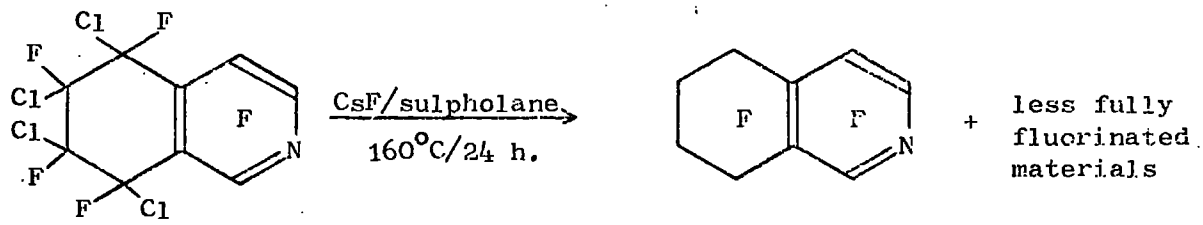
Now caesium fluoride is not very soluble in sulpholane, and it is believed that reaction occurs on the surface of the solid, where the sulpholane solvates the caesium ions, leaving the fluoride ions relatively free and reactive. If this is so, caesium fluoride impregnated with a little sulpholane should be a useful fluorinating agent, and it was tried here.

Reaction between the liquid 5,6,7,8-tetrachloroheptafluoroquinoline and sulpholane doped caesium fluoride gave a mixture, which the mass spectrum showed was a mixture of partially and fully fluorinated compounds.



From this mixture it was possible to separate perfluoro-5,6,7,8-tetrahydroquinoline, so this experiment has also demonstrated the feasibility of using sulpholane doped caesium fluoride as a fluorinating reagent.

(ii) 5,6,7,8-Tetrachloroheptafluoroisoquinoline. Fluorination of this liquid compound was also attempted by stirring with sulpholane doped caesium fluoride and, as in the case of the quinoline ring system, a mixture of partially and fully fluorinated compounds was produced.



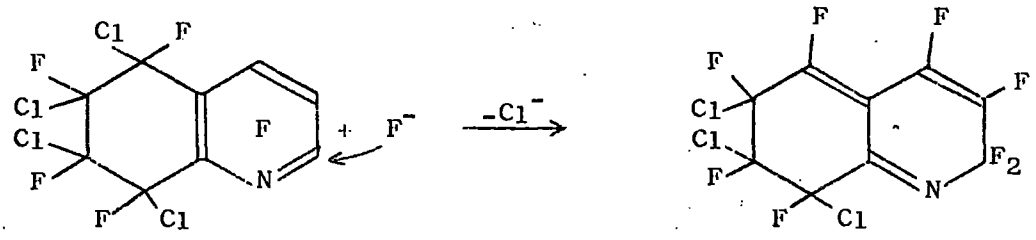
Separation of a sample of perfluoro-5,6,7,8-tetrahydroisoquinoline was achieved by preparative scale vapour phase chromatography.

C. Conclusions

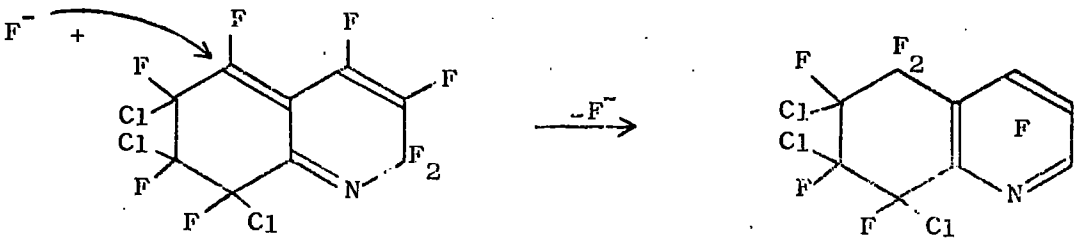
The conversion of 5,6,7,8-tetrachloroheptafluoroquinoline to perfluoro-5,6,7,8-tetrahydroquinoline, by halogen exchange in a solvent, provides further evidence for the proposed mechanism of the formation of the latter during autoclave fluorinations of heptachloroquinoline. The preparation of 5,6,7,8-tetrachloroheptafluoroisoquinoline, and its conversion to perfluoro-5,6,7,8-tetrahydroisoquinoline, suggest that a similar mechanism may apply to the isoquinoline ring system.

However, it is not immediately clear why these halogen exchange reactions occur at all, for simple S_N2 displacement of chlorine by fluorine at an sp^3

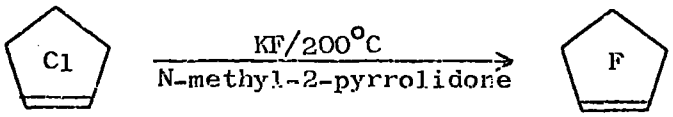
hybridised carbon is difficult. It is possible that reaction occurs via attack in the heteroaromatic ring, as is shown below for the case of quinoline.



Rearomatisation may then occur by attack at the 5-position.

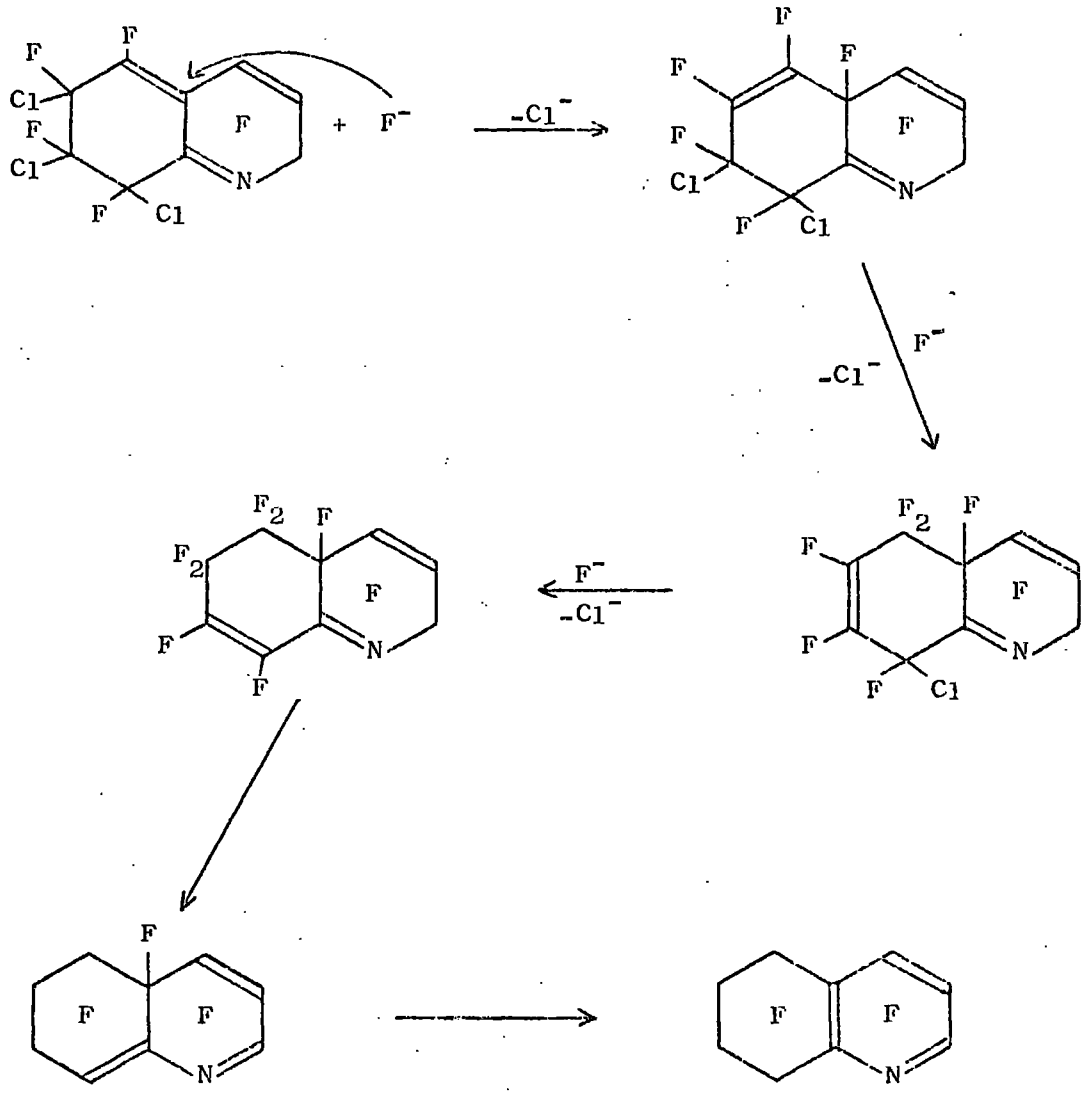


Alternatively, replacement of all the chlorine atoms may be achieved by migration of the double bond around the carbocyclic ring, as is shown in Figure 5-2. The initial attack in the heterocyclic ring could occur in another position and it is clear that, by this kind of process, all the chlorine atoms can be replaced by fluorine, with only aromatic and vinylic attack occurring. A similar mechanism is obviously possible for the isoquinoline ring system and such a mechanism has been proposed for the easy preparation of octafluorocyclopentene from octachlorocyclopentene by halogen exchange in a solvent.[214]



If this is the mechanism for the conversions of 5,6,7,8-tetrachloro-heptafluoroquinoline and -isoquinoline to perfluoro-5,6,7,8-tetrahydroquinoline

FIGURE 5-2

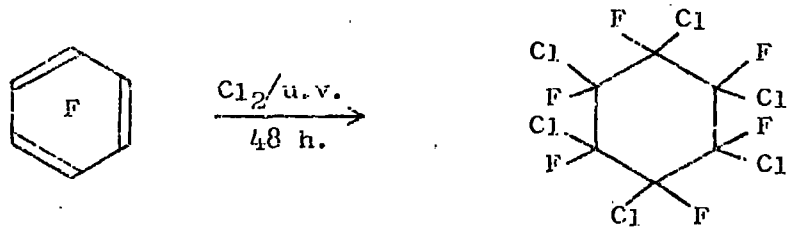


and -isoquinoline, then a molecule like 1,2,3,4,5,6-hexachlorohexafluoro-cyclohexane should be completely unaffected by the same fluorinating agent.

2.2 Fluorination of 1,2,3,4,5,6-Hexachlorohexafluorocyclohexane

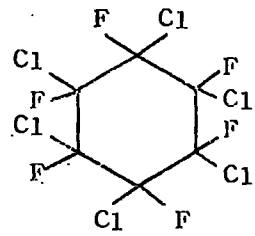
A. Preparation

This compound was prepared by reaction between chlorine gas and hexafluorobenzene, under the influence of ultra-violet light, as described in the literature.[215]



B. Reaction with Sulpholane Doped Caesium Fluoride

Reaction of 1,2,3,4,5,6-hexachlorohexafluorocyclohexane with sulpholane doped caesium fluoride, under the same conditions as those needed for the fluorination of 5,6,7,8-tetrachloroheptafluoroquinoline and -isoquinoline, gave no reaction.



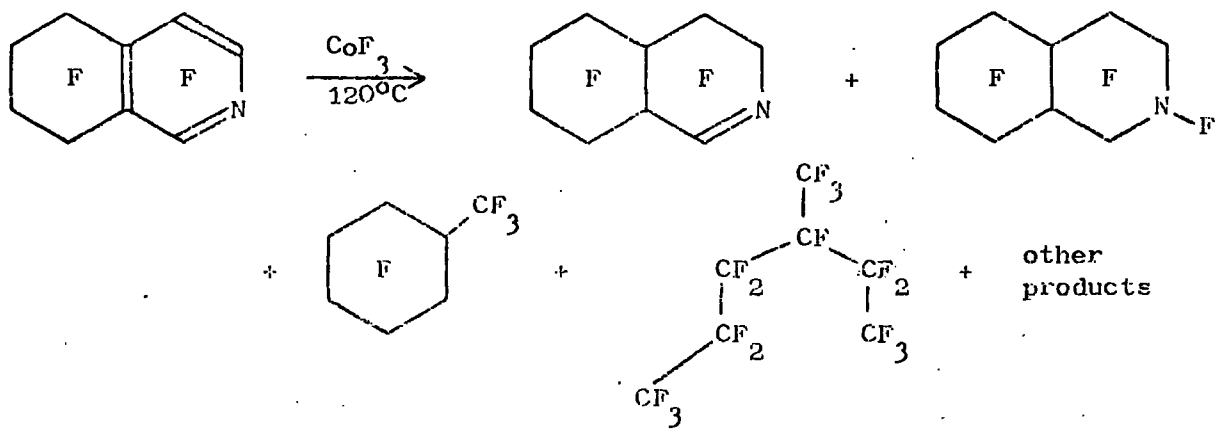
$\xrightarrow[160^{\circ}C/24\ h.]{CsF/sulpholane}$ No reaction

This provides further evidence that the fluorinations of the quinoline and isoquinoline compounds proceed by a mechanism, such as that given above, which does not involve simple S_N2 displacement.

3. Reactions of Perfluoro-5,6,7,8-tetrahydroisoquinoline

3.1 Fluorination with Cobalt Trifluoride

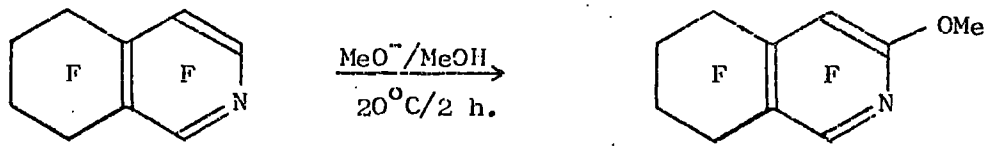
As mentioned before, perfluoro-5,6,7,8-tetrahydroisoquinoline can be obtained from heptafluoroisoquinoline by fluorination with cobalt trifluoride, so further reaction with this reagent was attempted with the hope of partially or fully saturating the heterocyclic ring, without ring opening. The material isolated was a seven component mixture and its separation was not attempted. Combined gas chromatography-mass spectroscopy, suggested that a lot of ring-opening and nitrogen loss was occurring.



3.2 Reactions with Methoxide Ion

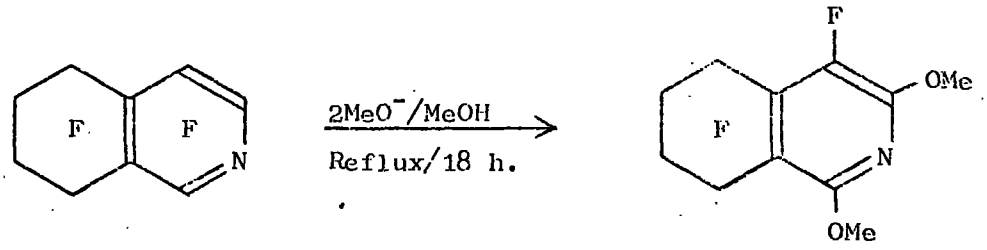
A. One Equivalent of Methoxide Ion

Perfluoro-5,6,7,8-tetrahydroisoquinoline reacted with one equivalent of methoxide ion to give a single monosubstituted product. The orientation of substitution in this case, and all others, was deduced from the ^{19}F n.m.r. spectrum (see section 5 of this chapter, below) and this product was shown to be 3-methoxyperfluoro-5,6,7,8-tetrahydroisoquinoline.



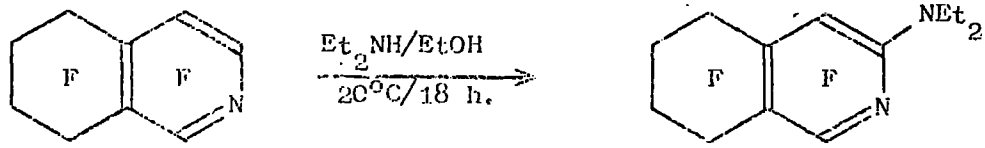
B. Two Equivalents of Methoxide Ion

It was possible to readily achieve disubstitution of perfluoro-5,6,7,8-tetrahydroisoquinoline by methoxide ion, and 1,3-dimethoxyperfluoro-5,6,7,8-tetrahydroisoquinoline was obtained alone.



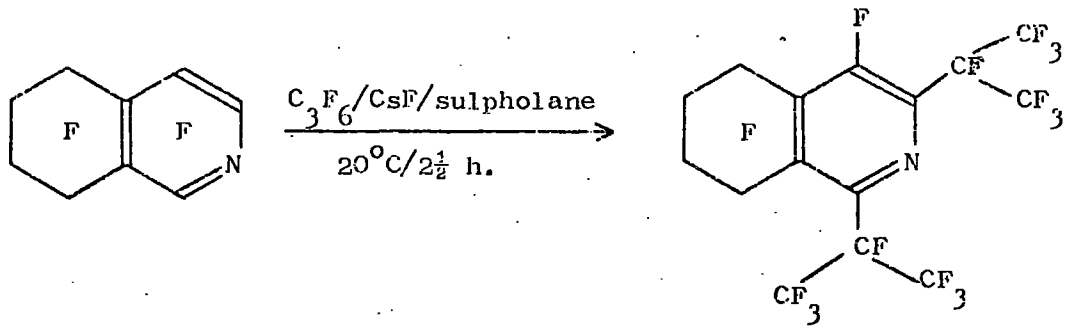
3.3 Reaction with Diethylamine

Perfluoro-5,6,7,8-tetrahydroisoquinoline reacted with one equivalent of diethylamine in alcoholic solution and gave a single product, which was 3-diethylaminoperfluoro-5,6,7,8-tetrahydroisoquinoline.



3.4 Reaction with Hexafluoropropene in the Presence of Fluoride Ion

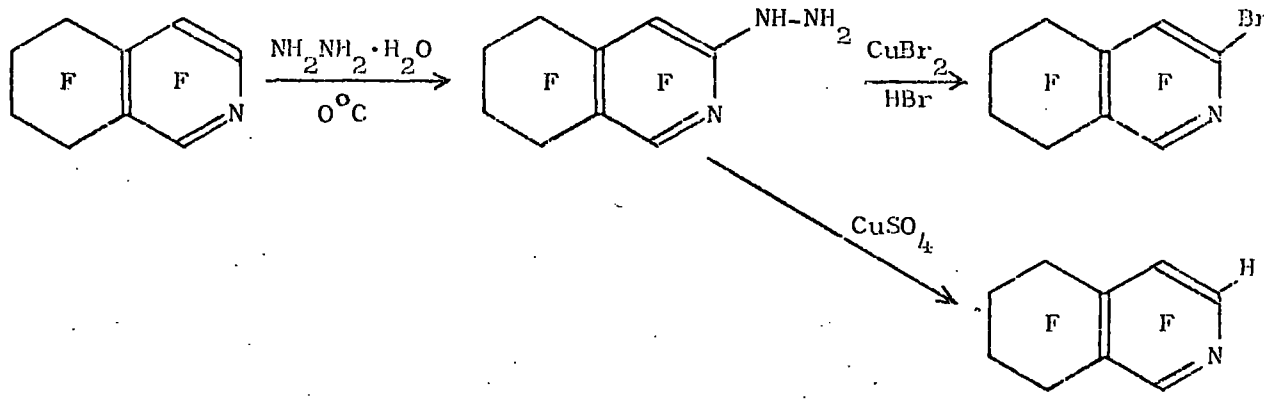
When caesium fluoride and perfluoro-5,6,7,8-tetrahydroisoquinoline in sulpholane were stirred under an atmosphere of hexafluoropropene, the expected polyfluoroalkylation reaction[182,183] occurred and perfluoro-5,6,7,8-tetrahydro-1,3-bisisopropylisoquinoline was produced.



3.5 Reactions with Hydrazine

Hydrazino derivatives of highly halogenated aromatic systems are not normally very stable, but they are valuable intermediates for the preparation of the corresponding hydro and bromo compounds. Thus aqueous copper sulphate replaces the hydrazino group by hydrogen,[216,217] and cupric bromide and hydrobromic acid replace the hydrazino group by bromine.[218] It was hoped that reaction of perfluoro-5,6,7,8-tetrahydroisoquinoline with hydrazine, followed by cupric bromide, would allow a bromo derivative to be obtained, from which a stable organolithium could possibly be prepared.

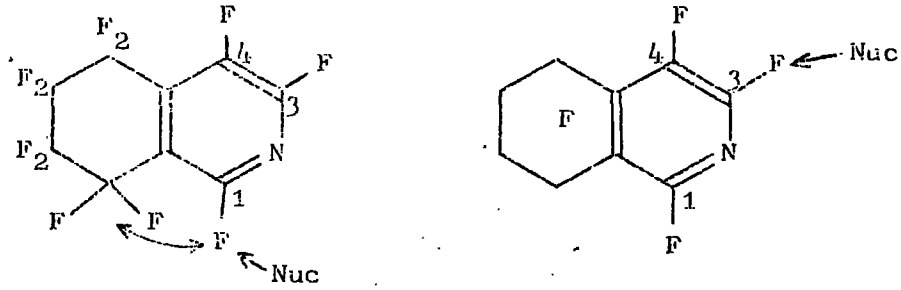
In practice it was found that the hydrazino derivative of perfluoro-5,6,7,8-tetrahydroisoquinoline was more than usually unstable and darkened as soon as it was formed, so that no pure products could be obtained. By treatment with cupric bromide and cupric sulphate, respectively, it was possible to obtain samples of a bromo and a hydro derivative in very low yield. The ^{19}F n.m.r. spectrum of the bromo derivative indicated that it was monosubstituted in the 3-position.



3.6 Rationalisation of Orientation

It is apparent that nucleophilic substitution of perfluoro-5,6,7,8-tetrahydroisoquinoline is most favoured in the 3-position, followed by the 1-position, which is not the characteristic orientation in isoquinoline systems, where the 1-position is the most reactive by a large amount. In fact, it is mechanistically unreasonable to regard the substrate as an isoquinoline, and it is more probable that it should be thought of as a dialkyl substituted pyridine. The nitrogen atom of a pyridine ring directs substitution to the positions ortho and para to the nitrogen atom, but in this case the para position is blocked by a perfluorocycloalkyl fragment, so substitution would be expected to occur at the positions ortho to the ring nitrogen atom. This is what does occur, but the influence of the ring nitrogen atom does not explain why substitution is more favoured in the 3-position than in the 1-position.

The directing influence of the fluorine atoms would tend to favour 3-substitution, because there is one fluorine atom ortho and one meta to the point of substitution, whereas there is one fluorine atom para and one meta to the 1-position, and it is believed that ortho fluorine atoms are more activating than para fluorine atoms.[116]



Steric effects would also favour substitution in the 3-position, so together with the effect of the fluorine atoms, they explain why substitution is preferred at the 3-position. It is not clear what effect the perfluorocycloalkyl fragments would have upon orientation, but it is not expected to be large enough to direct substitution away from the 3-position, and this is not observed experimentally.

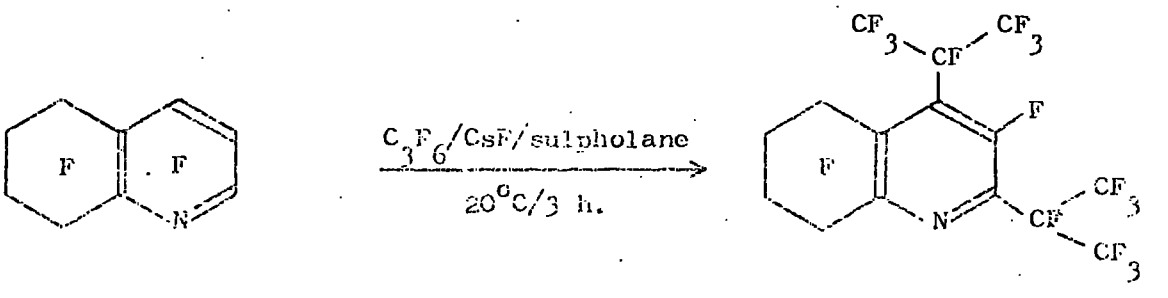
4. Reactions of Perfluoro-5,6,7,8-tetrahydroquinoline

Treating this compound, too, as a dialkyl substituted pyridine, the positions which are activated to nucleophilic attack by the ring nitrogen atom are the 2- and 4-positions.

When substitution occurs in either position there is one fluorine atom ortho, and one meta, to the point of substitution, so the fluorine atoms are not likely to direct nucleophiles preferentially to one of these positions. As in the case of the isoquinoline analogue, the orienting influence of the perfluorocycloalkyl fragments is unclear, but steric effects would clearly cause 2-substitution to be favoured over 4-position.

As described in section 1.3, substitution of perfluoro-5,6,7,8-tetrahydroquinoline by simple nucleophiles occurs in both 2- and 4-positions at a similar rate. This is consistent with the above predictions, and shows that the combination of orienting factors arising from the perfluorocycloalkyl fragments and steric effects, is not very large.

A reaction of perfluoro-5,6,7,8-tetrahydroquinoline with hexafluoropropene in the presence of fluoride ion was attempted, and perfluoro-5,6,7,8-tetrahydro-2,4-bisisopropylquinoline was produced.



5. ^{19}F N.M.R. Spectra

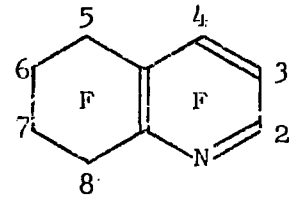
5.1 Spectra of Perfluoro-5,6,7,8-tetrahydroquinoline and -isoquinoline

Table 5-1 shows the spectrum of perfluoro-5,6,7,8-tetrahydroquinoline, which has already been measured and partially assigned.[219]

Table 5-2 shows the spectrum of perfluoro-5,6,7,8-tetrahydroisoquinoline, which has also already been measured and partially assigned.[207]

TABLE 5-1

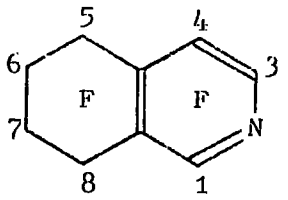
^{19}F N.M.R. Spectrum of Perfluoro-5,6,7,8-tetrahydroquinoline



Shift p.p.m.	Assignment
72·9	2
108·8	CF_2
113·1	CF_2
118·2	4
136·2	CF_2
137·0	CF_2
155·8	3

TABLE 5-2

^{19}F N.M.R. Spectrum of Perfluoro-5,6,7,8-tetrahydroisoquinoline



Shift p.p.m.	Assignment
65·2	1
77·4	3
about 110	CF_2 5 and 8
134·0	CF_2 6 and 7
144·6	4

5.2 Spectra of Substituted Perfluoro-5,6,7,8-tetrahydroisoquinolines

A. Simple Substituents

Generally the replacement of one or two fluorine atoms by some other group did not greatly alter the chemical shifts of the remaining ring fluorine atoms, so the positions of the substituents could be identified by comparing the observed spectrum with the known spectrum of the parent perfluoro-5,6,7,8-tetrahydroisoquinoline.

(i) Monosubstitution. Monosubstitution was shown to be at the 3-position because the monosubstituted products had no peaks in the region of 77 p.p.m., whereas there were peaks at about 65 p.p.m. and 145 p.p.m., corresponding to the 1- and 4-fluorine atoms, respectively.

Coupling between the 1- and 4-fluorine atoms was about 30 Hz., between 4- and 5- it was about 20 Hz., and between 1- and 8- it was also about 20 Hz., so that the 1- and 4-fluorine atoms generally appeared as doublets of triplets.

Coupling between fluorine atoms in the carbocyclic ring was small and unresolved, so that the 5- and 8-fluorine atoms appeared as doublets of broad peaks, and the 6- and 7-fluorine atoms appeared as a broad singlet.

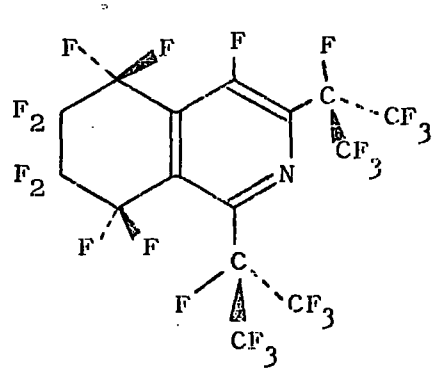
(ii) Disubstitution. Disubstitution was shown to be at the 1- and 3-positions because the disubstituted compounds had no peaks with a chemical shift of less than 100 p.p.m., while the 4-fluorine atom, with a shift of about 145 p.p.m., could be seen.

Coupling between the 4- and 5-fluorine atoms was again about 20 Hz., and again coupling around the carbocyclic ring was small and unresolved. Therefore, the 4-fluorine atom appeared as a triplet, the 5-fluorine atoms as a doublet of broad peaks, the 6- and 7-fluorine atoms as a broad singlet, and the 8-fluorine atoms as a broad singlet.

B. Substitution by Heptafluoroisopropyl Groups

The spectrum of the disubstituted compound is consistent with substitution having occurred in the 1- and 3-positions, and with the 4-fluorine atom having a much lower chemical shift than in the parent compound.

The fluorine atoms of the trifluoromethyl groups appear as sharp singlets, indicating that the isopropyl groups are not at all free to rotate and that the molecule exists in the preferred conformation shown below.

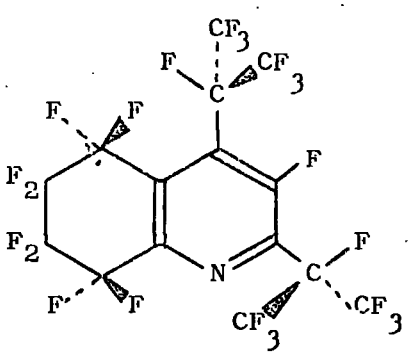


Coupling in the carbocyclic ring is small and unresolved, so that the 6- and 7-fluorine atoms appear as a broad singlet, while the tertiary fluorine in

the 1-position couples with the 8-fluorine atoms by 76 Hz., so that the former is a triplet and the latter is a doublet of broad peaks. The tertiary fluorine in the 3-position couples with the 4-fluorine atom, making it a doublet, and the 5-fluorine atoms also appear as a doublet of broad peaks because of coupling to the 4-fluorine atom. The 4-fluorine atom, which couples with the 5-fluorine atoms and the tertiary fluorine in the 3-position, is a doublet of triplets. There seem to be some second order complexities associated with the 5-fluorine atoms.

5.3 Spectrum of Perfluoro-5,6,7,8-tetrahydro-2,4-bisisopropylquinoline

The spectrum of this disubstituted compound is consistent with the assignment of the two heptafluoroisopropyl groups to the 2- and 4-positions. Again, there is only small coupling around the carbocyclic ring, which is unresolved, but the trifluoromethyl resonances show some complexities, indicating that there is some hindered rotation of the heptafluoroisopropyl groups, but that the most favoured orientation is as shown below.



The tertiary fluorine atom in the 4-position couples with the 5-fluorine atoms, so that the latter appear as a doublet of broad peaks. The tertiary fluorine atom in the 2-position couples with the 3-fluorine atom, but overlaps with the other tertiary fluorine atom, so that only three rather broad peaks are seen in the tertiary region of the spectrum. The 3-fluorine atom appears as an unresolved complex peak with a much smaller chemical shift

than in the parent perfluoro-5,6,7,8-tetrahydroquinoline. The 6-, 7- and 8-carbocyclic fluorine atoms all apear as broad, unresolved singlets.

EXPERIMENTAL

CHAPTER VI

Experimental Work

1. General

1.1 Chemicals

Heptachloroquinoline, heptachloroisoquinoline, heptafluoroquinoline and heptafluoroisoquinoline were synthesised by the usual procedures.[20] A small sample of 9-chloroacridine was obtained from Phase Separations Ltd., while 9-acridanone and 7,8-benzoquinoline were purchased from Aldrich Chemical Company Inc. Hexafluoropropene was obtained from Peninsular Chemical Research Inc., and hexafluorobenzene from Bristol Organics Ltd. Octachloronaphthalene was donated by I.C.I. Ltd.

n-Butyl lithium was supplied as, theoretically, a 2·2M solution in n-hexane and it was stored under an atmosphere of dry nitrogen. It was standardised by the procedure described in Chapter III and section 3.4. of this chapter.

Potassium fluoride was dried by heating in the air, grinding and then heating under vacuum. It was stored under an atmosphere of dry nitrogen. Caesium fluoride was dried by slowly warming under vacuum and periodically grinding in a nitrogen glove bag. It, too, was stored under an atmosphere of dry nitrogen.

1.2 Solvents

Sulpholane was purified by collecting the middle fraction in a vacuum distillation. It was stored above room temperature, under an atmosphere of dry nitrogen, and over type 4A molecular sieve.

Chloroform was dried by refluxing with phosphorus pentoxide under dry nitrogen and then distilling onto type 4A molecular sieve; it was stored over this sieve and under an atmosphere of dry nitrogen.

Methanol was dried by reaction of one litre with 10g. magnesium, followed by distillation; it too was stored under an atmosphere of dry nitrogen gas.

1.3 Instruments

Infra-red spectra were recorded on a Grubb-Parsons 'Spectromaster' or a Perkin-Elmer 457 spectrophotometer. The samples were prepared as discs with potassium bromide or, for liquids or low melting solids, as a contact film between potassium bromide plates.

Ultra-violet spectra were recorded on Pye-Unicam SP800 or SP8000 spectrophotometers.

Mass spectra were recorded on an A.E.I. MS9 Spectrometer or on a V.G. Micromass 12B, fitted with a Pye 104 gas chromatograph and quoted molecular weights are from mass spectroscopic measurements, as are the number of chlorine atoms in the molecule.

Analytical gas phase chromatography was carried out on a Griffin and George D6 Gas Density Balance. Preparative scale gas phase chromatography was achieved on a Varian 'Aerograph'. For all gas phase chromatography measurements the column used was of silicone elastomer on Celite, which is known as Column 'O'.

Thin layer chromatographs were recorded on thin glass plates coated with an even layer of silica (Silic gel/CT, Reeve Angel Scientific Ltd.), containing a fluorescing agent. The position of compounds on the plate was revealed by the way they quenched the fluorescence normally excited by ultra-violet light.

Proton and fluorine nuclear magnetic resonance spectra were recorded on a Varian 56/60D spectrometer at the ambient probe temperature ($40^{\circ}C$). For protons, T.M.S. was used as external standard and downfield shifts are recorded as positive. For fluorine, fluorotrichloromethane was used as

external standard, and upfield shifts are recorded as positive. Carbon-13 spectra of natural abundance samples were recorded on a Bruker HX90 with Fourier Transform facility.* Natural abundance T.M.S. was used as reference and all shifts are downfield.

1.4 Analyses

Carbon, hydrogen and nitrogen analyses were carried out on a Perkin-Elmer 240 Elemental Analyser. Analysis for halogen was a slightly modified version of the method described in the literature.[220] Sulphur analyses were achieved by a modified form of the oxygen flask combustion method.[221] †

Melting points and boiling points were determined at atmospheric pressure and are uncorrected. Boiling points were measured by the Siwoloboff method.

2. Experimental for Chapter II - Syntheses of Some Perchloroheterocyclic Compounds Containing Nitrogen

2.1 Preparation of Starting Materials

A. 9-Chloroacridine

(i) Conversion of 9-Acridanone to 9-Chloroacridine. 9-Acridanone (60g., 308 mmole), phosphoryl chloride (300g., 180 ml., 1954 mmole) and concentrated sulphuric acid (5 ml.) were refluxed together for 4 h. Excess phosphoryl chloride was then removed by distillation under reduced pressure and the residue added to a mixture of crushed ice (500g.), ·880d ammonia solution (200 ml.) and chloroform (200 ml.). This mixture was well stirred, the chloroform layer was separated and the aqueous layer was extracted with more chloroform (100 ml.). The combined chloroform layers were dried with anhydrous calcium chloride; after filtration the solvent was removed from the filtrate to give a brown solid. Upon recrystallising from ethanol, yellow crystals of 9-chloroacridine, which darkened on standing, were produced. (Yield = 63g., 95%). M.p. 120°C; literature value 119-120°C.[174]

* By the S.R.C. Physico-Chemical Measurements Unit

† By the Analytical Services of the Chemistry Department

(Identification was by a comparison of the infra-red spectrum with that of the commercial sample).

(ii) Conversion of Diphenylamine-2-carboxylic Acid to 9-Chloroacridine. Diphenylamine-2-carboxylic acid (50g., 235 mmole) and phosphoryl chloride (270g., 160 ml., 1758 mmole) were refluxed together for 2 h. The resulting mixture was worked up as in (i) above by distillation and addition to ice. (Yield of crude 9-chloroacridine = 35g., 70%).

(iii) Preparation of Diphenylamine-2-carboxylic Acid. 2-Chlorobenzoic acid (41g., 262 mmole), potassium carbonate (41g., 325 mmole), aniline (155g., 1666 mmole) and cupric oxide (1g.) were refluxed together for 3 h. The excess aniline was then removed by steam distillation, decolourising charcoal (20g.) was added and the mixture was boiled for 15 m. After hot filtration, the filtrate was cautiously added, with stirring, to a mixture of concentrated hydrochloric acid (30 ml.) and water (60 ml.). Pale pink diphenylamine-2-carboxylic acid was precipitated. (Yield = 54 g., 95%). M.p. 174-175°C., literature value 179-181°C.[176] Identification was by molecular weight (213) and infra-red spectrum (N-H absorbtion at 3·0μ, O-H absorbtion centred on 3·5μ and C=O absorbtion at 6·0μ).

B. 6-Chlorophenanthridine

(i) Conversion of Diphenic Acid to Diphenic Anhydride. Diphenic acid (250g.) and acetic anhydride (750 ml.) were heated at 120°C for 1½ h. The white solid produced after cooling is diphenic anhydride. It was filtered off, washed with glacial acetic acid and dried under vacuum. (Yield = 210g., 90%). M.p. 219-222°C; literature value 212°C.[177] Identification was by molecular weight (224) and infra-red spectrum (no O-H absorbtions, two C=O absorbtions at 5·68μ and 5·77μ).

(ii) Conversion of Diphenic Anhydride to Diphenamic Acid. Diphenic

anhydride (210g.) and ·880d ammonia solution (420 ml.) were refluxed together until all the solid had dissolved; this took about 2 h. The mixture was then cooled and cautiously acidified by adding concentrated hydrochloric acid, with stirring. Diphenamic acid was precipitated. (Yield = 175g., 83%). M.p. 186-188°C; literature value 190°C.[177] Identification was by molecular weight (223) and infra-red spectrum (O-H absorbtion centred on 3·5μ, weak C≡N absorbtion at 4·25μ and C=O absorbtion at 5·89μ).

(iii) Conversion of Diphenamic Acid to 6-Phenanthridanone. A solution of bromine (35·7 ml., 700 mmole) in 10% sodium hydroxide solution (980 ml.) was prepared. Then diphenamic acid (175g., 784 mmole) was dissolved in 10% sodium hydroxide solution (700 ml.), and the bromine solution was added slowly, but immediately. The mixture was allowed to stand for half an hour and then concentrated sodium hydrogen sulphite solution (35 ml.) was added. The resulting mixture was acidified with concentrated hydrochloric acid (280 ml.) which caused a brown solid to be precipitated. This was very crude 6-phenanthridanone, which was filtered off and washed well with water. Recrystallisation from ethanol produced off white crystals of quite pure 6-phenanthridanone. (Yield = 53g., 35%). M.p. 282-283°C; literature value 291°C.[177] Identification was by molecular weight (195) and infra-red spectrum (N-H absorbtion at 3·15μ and C=O absorbtion at 6·01μ). Ultra-violet spectrum No. 1.

(iv) Conversion of 6-Phenanthridanone to 6-Chlorophenanthridine. 6-Phenanthridanone (50g.), phosphoryl chloride (500 ml.), N,N-dimethylaniline (20 ml.) and concentrated sulphuric acid (5 ml.) were refluxed together for 3 h. The excess phosphoryl chloride was then removed by distillation under reduced pressure and the residue cautiously added to a mixture of crushed ice (1 kg.), ·880d ammonia solution (500 ml.) and chloroform (500 ml.). After well stirring, the chloroform layer was separated and the aqueous layer

extracted with more chloroform (100 ml.). The combined chloroform layers were dried over anhydrous calcium chloride and then filtered. The solvent was removed from the filtrate to leave a dark residue; when recrystallised from ethanol, this gave yellow crystals of 6-chlorophenanthridine. (Yield = 38g., 69%). M.p. 110-112°C; literature value 116°C.[171] Identification was by molecular weight (213 (Cl = 35) with one chlorine atom) and infra-red spectrum (no N-H, O-H or C=O absorbtions, C-Cl absorbtion at 13·24 μ).

2.2 Chlorination Reactions

A. 9-Chloroacridine

The method used for all successful chlorinations was the same and the quantitative differences between the various runs are summarised in Table 6-1. The most economical and successful run was run 3. In this run, 9-chloroacridine (60g.) and finely crushed aluminium chloride (200g.) were placed in a flask fitted with a gas inlet, air condenser and teflon-bladed paddle stirrer. All the apparatus had been rinsed with acetone before use and dried in the oven. Both before and during the reaction a continuous stream of dry nitrogen gas was passed through the flask. The flask was warmed to 100°C, which caused a molten complex between 9-chloroacridine and aluminium chloride to be formed, and stirring was begun, although initially the complex was very viscous. Stirring was continued for 48 h. while the temperature was 120-160°C and dry chlorine gas (265g.) was passed into the space above the reaction mixture. For a further 48 h. stirring was continued with the temperature at 170-190°C and more chlorine gas (335g.) was added.

Dry chloroform (1000 ml.) was added to the stirred molten mixture and the resulting mixture was refluxed and stirred until most of the material was in solution. This solution was a deep red colour and, as far as possible,

TABLE 6-1

Aluminium Chloride Catalysed Chlorinations of 9-Chloroacridine

Reaction	1	2	3	4	5
Amount of 9-Chloroacridine	35g.	33g.	60g.	45g.	50g.
Amount of Aluminium Chloride	100g.	100g.	200g.	170g.	180g.
Temperature for 1st 48 h.	120-140°C	120-150°C	120-160°C	120-150°C	130-150°C
Amount of Chlorine in 1st 48 h.	295g.	895g.	265g.	500g.	2120g.
Temperature for 2nd 48 h.	140-160°C	160-190°C	170-190°C	160-180°C	160-180°C
Amount of Chlorine in 2nd 48 h.	480g.	355g.	335g.	310g.	40g.
Amount of dry Chloroform	1000 ml.	1500 ml.	1000 ml.	1000 ml.	1000 ml.
Amount of dry Methanol	500 ml.	1000 ml.	500 ml.	500 ml.	500 ml.
Yield of Nona-chloroacridine	40%	30%	75%	65%	45%

it was handled only under dry nitrogen gas. After filtration, the solution was cooled to -10°C and dry methanol (500 ml.), also cooled to -10°C, was added. This mixture was stirred and kept cool until the red colour had disappeared and a yellow precipitate was formed. The precipitate was fairly pure nonachloroacridine. (Yield = 104g., 75%). M.p. 246-249°C.

A Soxhlet extraction was carried out on some of this material (5g.) in a thoroughly dried extraction apparatus, using dry chloroform (200 ml.) as the solvent. After extraction, the chloroform layer was cooled and the

resulting pale yellow crystals of analytically pure nonachloroacridine were filtered off. M.p. 251-253°C. (Found: C, 31·7; N, 3·1; Cl 64·8%. $C_{13}NCl_9$ requires C, 31·91; N, 2·86; Cl, 65·22%). Molecular weight = 485 (Cl = 35, see Appendix 2) with nine chlorine atoms. Infra-red spectrum No. 1. Ultra-violet spectrum No. 2.

B. 6-Chlorophenanthridine

The procedure used for all successful chlorinations was the same; the quantitative details are given in Table 6-2. Run 1 is typical and is described here. All the apparatus was dried before using by rinsing with acetone and drying in the oven; both before and during the reaction it was continually purged with dry nitrogen gas. 6-Chlorophenanthridine (42g.) and finely powdered aluminium chloride (180g.) were placed in a flask fitted with air condenser, teflon-bladed paddle stirrer and gas inlet. The flask was warmed to 120°C and the resulting molten complex was stirred. The temperature was maintained at 120-150°C for 48 h., while stirring was continued and dry chlorine gas (95g.) was passed into the space above the reaction mixture. The temperature was then raised for 48 h. to 160-180°C; stirring was continued and more chlorine gas (185g.) was passed in.

Dry chloroform (1000 ml.) was added to the stirred molten mixture and the resultant was refluxed until all soluble material had dissolved to give a deep red solution. This solution was handled, as far as possible, only under dry nitrogen gas. It was filtered, cooled to -10°C and then dry methanol (750 ml.), also cooled to -10°C, was added. This mixture was stirred and kept cool until the red colouring had disappeared and a yellow precipitate formed. This was analytically pure nonachlorophenanthridine, without further treatment. (Yield = 70g., 73%). M.p. 255-257°C. (Found: C, 31·6; Cl, 64·7%. $C_{13}NCl_9$ requires C, 31·91; Cl, 65·22%). Molecular weight 485 (Cl = 35) with nine chlorine atoms. Infra-red spectrum No. 2. Ultra-violet spectrum No. 3.

TABLE 6-2

Aluminium Chloride Catalysed Chlorinations of 6-Chlorophenanthridine

Reaction	1	2
Amount of 6-Chlorophenanthridine	42g.	25g.
Amount of Aluminium Chloride	180g.	120g.
Temperature for 1st 48 h.	120-150°C	130-150°C
Amount of Chlorine in 1st 48 h.	95g.	155g.
Temperature for 2nd 48 h.	160-180°C	160-180°C
Amount of Chlorine in 2nd 48 h.	185g.	75g.
Amount of dry Chloroform	1000 ml.	1000 ml.
Amount of dry Methanol	750 ml.	500 ml.
Yield	50%	65%

C. 7,8-Benzoquinoline

(i) Aluminium Chloride Catalysed Elemental Chlorination. The apparatus for the chlorination was rinsed with acetone and dried in an oven before use; before and during the reaction it was continually purged with dry nitrogen gas. 7,8-Benzoquinoline (50g.) and finely crushed aluminium chloride (180g.) were placed in a flask fitted with teflon-bladed paddle stirrer, air condenser and gas inlet. The flask was warmed until a molten complex was formed between the reactants at 130°C, whereupon stirring was begun. The temperature was maintained at 140-160°C for 48 h. while the mixture was stirred and dry chlorine gas (450g.) was passed into the space above the reaction mixture. The temperature was then raised to 160-180°C for another

48 h. while stirring was continued and more chlorine (135g.) was added.

At the end of this time, the hot, molten mixture was cautiously poured onto ice-water (1500 ml.), and well stirred. The reddish-brown solid obtained by filtration was a mixture of chlorinated 7,8-benzoquinolines, chiefly pentachloro-7,8-benzoquinoline and hexachloro-7,8-benzoquinoline. (Yield = 90g., ~85%). M.p. 140-144°C. (Found: Cl, 53·2%. $C_{13}NH_3Cl_6$ requires Cl, 55·2%. $C_{13}NH_4Cl_5$ requires Cl, 50·6%). Identification was by the mass spectrum. (Parent peaks at 383 with six chlorine atoms and at 349 with five chlorine atoms). Infra-red spectrum No. 3.

(ii) Further Chlorination with Phosphorus Pentachloride. The partially chlorinated 7,8-benzoquinolines obtained in section (i) above (10g.) and phosphorus pentachloride (150g.) were sealed in a steel autoclave, which was then evacuated. The autoclave was placed in a furnace, heated to 370°C, and heating was maintained at this temperature until 6 h. after the autoclave had originally been put in the furnace. The autoclave was then vented, allowed to cool, opened, and the contents were stirred with ice-water (400 ml.). The solid which was filtered from this solution was crude nonachloro-7,8-benzoquinoline.

A pure sample of nonachloro-7,8-benzoquinoline was obtained by sublimation under vacuum. M.p. 209-211°C. (Found: Cl, 65·1%. $C_{13}NCl_9$ requires Cl, 65·22%. Incomplete oxidation made it impossible to obtain satisfactory carbon analysis). Molecular weight = 485 with nine chlorine atoms. Infra-red spectrum No. 4. Ultra-violet spectrum No. 4.

3. Experimental for Chapter III - Properties of Some Perchloroheterocyclic Compounds Containing Nitrogen

3.1 Attempted Fluorination Reactions

A. Nonachloroacridine

The general fluorination procedure was the same in all cases and

quantitative details of the various reactions are given in Table 6-3. Run 4 is typical and is described here. Nonachloroacridine (30g.) and dry potassium fluoride (200g.) were well mixed and sealed as rapidly as possible in a thoroughly dried 120 ml., nickel-lined autoclave. The autoclave was then evacuated and heated at 350°C for 18 h.

TABLE 6-3

Autoclave Fluorinations of Nonachloroacridine

Reaction	Amount of Nonachloroacridine	Amount of Dry Potassium Fluoride	Reaction Time	Reaction Temperature
1	25g.	140g.	24 h.	470°C
2	25g.	160g.	18 h.	350°C
3	23g.	150g.	18 h.	300°C
4	30g.	200g.	18 h.	350°C
5	30g.	200g.	18 h.	400°C
6	30g.	200g.	18 h.	400°C
7	20g.	160g.	18 h.	400°C

Volatiles were then transferred out of the hot autoclave, under vacuum, into a cold trap. Only materials which were gaseous at room temperature were obtained in this way. After cooling, the autoclave was let down to an atmosphere of dry nitrogen gas, and opened. It was found to contain a powdery black residue, from which it was attempted to extract tractable material in various ways.

Sublimation under 0·01 mm. Hg. at 160°C gave only very small amounts of a material which was chiefly tetrachlorotetrafluoro-9-acridanone. (Identified by the mass spectrum, with $^{m}/e = 403$ and four chlorine atoms).

Some of the black residue from the autoclave (50g.) was refluxed with acetone, chloroform or chlorobenzene (500 ml.) for 2 h. The cooled mixture

was filtered and the solvent was removed from the filtrate to give a very small amount of an orange solid, which was shown by the mass spectrum to be chiefly tetrachlorotetrafluoro-9-acridanone.

The rest of the residue from the autoclave was vigorously stirred with water (400 ml.) for 24 h., to leave a black polymeric solid.

B. Nonachlorophenanthridine

(i) In a Solvent. The general procedure for all these reactions was the same and the quantitative details are given in Table 6-4.

TABLE 6-4

Solvent Fluorinations of Nonachlorophenanthridine

Run	1	2	3	4
Fluorinating Agent	CsF	KF	KF	CsF
Amount of Fluorinating Agent	30g.	15g.	25g.	15g.
Amount of Nonachlorophenanthridine	5g.	3g.	3g.	2g.
Amount of dry Sulpholane	40 ml.	20 ml.	50 ml.	40 ml.
Temperature	160°C	160°C	160°C	180°C
Time	24 h.	24 h.	90 h.	24 h.

Run 4 is typical and is described here.

All the apparatus was rinsed with acetone and thoroughly dried in an oven before use. Nonachlorophenanthridine (2g., 4·1 mmole), dry caesium fluoride (15g., 98·9 mmole), and dry sulpholane (40 ml.) were placed in a flask fitted with a magnetic stirrer, gas-tap and variable volume reservoir (conveniently a football bladder), to allow for expansion. The flask was evacuated to de-gas the solvent and then let down to an atmosphere of dry nitrogen gas. The contents were stirred at 180°C for 24 h.

After cooling, the resulting mixture was poured onto water (4000 ml.) and well stirred. The solid was filtered off and refluxed with chloroform (200 ml.) for 1½ h. This mixture was filtered, and the solvent was removed from the filtrate to leave a pale brown solid, which was a mixture of chlorofluoro-6-phenanthridanones. (Identified by the mass spectrum; peaks at 403 with four chlorine atoms, 419 with five chlorine atoms, 435 with six chlorine atoms, and so on).

(ii) In the Solid Phase. The general procedure was the same in all cases and the quantitative details of the various runs are given in Table 6-5. Run 2, which is typical, is described here.

TABLE 6-5

Autoclave Fluorinations of Nonachlorophenanthridine

Run	1	2	3
Amount of Dry Potassium Fluoride	80g.	80g.	80g.
Amount of Nonachlorophenanthridine	8g.	8g.	8g.
Temperature	450°C	400°C	350°C
Time	3 h.	1½ h.	1¾ h.

Nonachlorophenanthridine (8g., 16·5 mmole) and dry potassium fluoride (80g., 1370 mmole) were well mixed and sealed in an autoclave, which was then evacuated. The autoclave was then heated at 400°C for 1½ h. Volatiles were then transferred out of the hot autoclave, under vacuum into a cold trap; these volatiles were all gaseous at room temperature.

The autoclave was then allowed to cool, let down to an atmosphere of dry nitrogen gas, and opened. The extraction of tractable material from the solid residue was attempted by the methods of vacuum sublimation, solvent

extraction and treatment with water, in a way analogous to that described for the fluorinations of nonachloroacridine, but without any success.

C. Nonachloro-7,8-benzoquinoline

The general procedure for the two reactions was the same and the quantitative details are given in Table 6-6.

TABLE 6-6

Autoclave Fluorinations of Nonachloro-7,8-benzoquinoline

Run	1	2
Amount of Dry Potassium Fluoride	20g.	20g.
Amount of Nonachloro-7,8-benzoquinoline	2g.	2g.
Temperature	450°C	350°C
Time	12 h.	6 h.

Run 2 is typical and is described here.

Nonachloro-7,8-benzoquinoline (2g., 4 mmole) and dry potassium fluoride (20g., 340 mmole) were well mixed and sealed in a 80 ml. nickel-lined steel tube. The tube was heated at 350°C for 6 h. and then cooled and opened, and the dark brown solid contents were emptied out. All attempts to isolate tractable material from this solid, by sublimation, solvent extraction, or treatment with water, as described for nonachloroacridine, failed.

3.2 Hydrolysis Reactions and Basicity

A. Nonachloroacridine

(i) Hydrolysis. Nonachloroacridine (2·0g.) was refluxed with water (50 ml.) and concentrated hydrochloric acid (50 ml.) for 18 h., and vigorously stirred. The green solid product was octachloro-9-acridanone. (Yield = 1·6g., 80%). M.p. > 340°C; literature value 370°C.[168] (Found:

C, 32·9; N, 2·8; Cl, 60·8%. Calculated for $C_{13}NHOCl_8$: C, 33·16; N, 2·98; Cl, 60·31%). Molecular weight = 467 with eight chlorine atoms. Infra-red spectrum No. 5. Ultra-violet spectrum No. 5.

(ii) Reaction with Hydrogen Chloride Gas. Nonachloroacridine (0·5g.) was dissolved in dry chloroform (450 ml.). The resulting solution was stirred and dry hydrogen chloride gas was bubbled through the solution until the uptake of gas had ceased. The yellow solid produced was filtered off, and the material isolated proved to be unchanged nonachloroacridine. (Identified by a comparison of its infra-red spectrum with that of an authentic sample from 2.2.A).

B. Hydrolysis of Nonachlorophenanthridine

Nonachlorophenanthridine (4·0g.) was stirred with water (30 ml.) and concentrated sulphuric acid (120 ml.) at 100°C for 100 h. After this time, the mixture was cooled and the solid was filtered off and washed well with water. Recrystallisation from chlorobenzene gave pure, green octachloro-6-phenanthridanone. (Yield = 2·4g., 62%). M.p. > 350°C. (Found: Cl, 60·5%. $C_{13}NHOCl_8$ requires Cl, 60·31%). Molecular weight = 467 with eight chlorine atoms. Infra-red spectrum No. 6. Ultra-violet spectrum No. 6.

3.3 Nucleophilic Substitution Reactions

A. Nonachloroacridine

(i) One Equivalent of Methoxide Ion. A solution of sodium (0·10g., 4·35 mmole) in dry methanol (5 ml.) was prepared and added to a suspension of nonachloroacridine (2·00g., 4·09 mmole) in dry methanol (150 ml.). The resulting mixture was refluxed for 24 h. and the green solid that was filtered off was octachloro-9-methoxyacridine. (Yield = 1·75g., 88%). M.p. 244-246°C. (Found: C, 35·0; N, 2·6; H, 0·8; Cl, 58·2%. $C_{14}NH_3OCl_8$ requires C, 34·68; N, 2·89; H, 0·62; Cl, 58·52%). Molecular weight = 481 with eight chlorine atoms. Infra-red spectrum No. 7.

Some of the octachloro-9-methoxyacridine (1·00g.) was stirred and refluxed with water (50 ml.) and concentrated hydrochloric acid (50 ml.) for 18 h. The solid product that was filtered off was octachloro-9-acridanone. (Identified by a comparison of its infra-red spectrum with that of an authentic sample from 3.2.A.(i)).

(ii) Two Equivalents of Methoxide Ion. The reaction was attempted at atmospheric pressure by first preparing a solution of sodium (0·12g., 5·20 mmole) in dry methanol (5 ml.). This solution was added to a suspension of nonachloroacridine (1·00g., 2·04 mmole) in dry methanol (70 ml.) and the resulting mixture was refluxed and stirred for 90 h. The green solid produced was octachloro-9-methoxyacridine. (Identified by a comparison of its infra-red spectrum with that of an authentic sample from 3.3.A.(i)).

The reaction under pressure was carried out by placing a solution of sodium (0·12g., 5·20 mmole) in dry methanol (30 ml.) in a nickel tube and adding nonachloroacridine (1·00g., 2·04 mmole). The tube was sealed and rotated in an oil bath at 200°C for 24 h. The tube was then cooled, opened, and the contents were washed out with methanol. A dark green solid was produced, which was octachloro-9-acridanone. (Identified by a comparison of its infra-red spectrum with that of an authentic sample from 3.2.A.(i)).

(iii) Diethylamine. Nonachloroacridine (1·00g.) was refluxed with diethylamine (70 ml.) for 24 h. The resulting mixture was cooled, poured onto water (100 ml.) and the solid was filtered off. This solid was recrystallised from chloroform to give orange octachloro-9-ethyliminoacridan. (Yield = 0·34g., 33%). M.p. 222-224°C. (Found: Cl, 56·6%. $C_{15}N_2H_6Cl_8$ requires Cl, 56·98%). Molecular weight = 494 with eight chlorine atoms. Infra-red spectrum No. 8. N.M.R. spectrum No. 1.

(iv) t-Butylamine. Nonachloroacridine (2·0g.) was stirred with refluxing t-butylamine (50 ml.) for 24 h., and then the cooled residue was

poured onto water (100 ml.). The solid produced was a mixture of starting material, octachloroacridines and substitution products. (Identified by the mass spectrum. Parent peaks at 485 with nine chlorine atoms, 451 with eight chlorine atoms, and 520 with eight chlorine atoms).

(v) Thiophenoxide Ion. Sodium (0·06g., 2·61 mmole) was added to dry, stirred methanol (100 ml.) and then thiophenol (2 ml.) was added, followed by nonachloroacridine (1·00g., 2·04 mmole), and the mixture was refluxed for $1\frac{1}{2}$ h. Water (50 ml.) was then added and the resulting solid was filtered off and recrystallised from chloroform to give a mixture of octachloroacridines. (Identified by the mass spectrum. Parent peak at 451 with eight chlorine atoms).

(vi) Hexafluoropropene in the Presence of Fluoride Ion. All the apparatus was rinsed with acetone and thoroughly dried in an oven before use. Nonachloroacridine (2·0g., 4·1 mmole), dry caesium fluoride (3g., 19·8 mmole) and dry sulpholane (40 ml.) were placed in a flask fitted with magnetic stirrer, gas-tap and variable volume reservoir. The apparatus was evacuated, the solvent was degassed, and then the apparatus was filled with hexafluoropropene (5g., 33·3 mmole). The mixture was stirred at 75°C for 3 h., during which time most of the gas was used up; stirring was continued at this temperature for another 16 h. Volatiles were then transferred out under vacuum into a cold trap, and the residue was mixed with water (300 ml.) and chloroform (300 ml.). The organic layer was separated, and the aqueous layer was extracted with more chloroform (2 x 100 ml.).

The combined chloroform layers were washed with water (3 x 100 ml.) and then dried with anhydrous magnesium sulphate. After filtration, the solvent was removed from the filtrate to leave octachloro-9-acridanone. (Identified by a comparison of its infra-red spectrum with that of an

authentic sample from 3.2.A.(i)).

B. Nonachlorophenanthridine

(i) Methoxide Ion. Nonachlorophenanthridine (1·00g., 2·04 mmole) was suspended in dry methanol (40 ml.) and sodium (0·06g., 2·60 mmole) was added. The resulting mixture was stirred and refluxed for 65 h. The cooled residue was added to water (40 ml.) and green octachloro-6-methoxyphenanthridine was filtered off. (Yield = 0·82g., 81%). M.p. 245-247°C. (Found: C, 34·4; N, 3·0; H, 0·6; Cl, 58·9%. $C_{14}NH_3OCl_8$ requires C, 34·68; N, 2·89; H, 0·62; Cl, 58·52%). Molecular weight = 481 with eight chlorine atoms. Infra-red spectrum No. 9.

Some of this octachloro-6-methoxyphenanthridine (0·7g.) was heated with water (30 ml.) and concentrated sulphuric acid (120 ml.) at 100°C for 110 h. The resulting mixture was cooled and the solid was filtered off and washed well with water. This was octachloro-6-phenanthridanone. (Identified by a comparison of its infra-red spectrum with that of an authentic sample from 3.2.B).

(ii) Diethylamine. Nonachlorophenanthridine (2·0g.) was stirred with refluxing diethylamine (50 ml.) for 65 h. The resulting mixture was stirred with water (100 ml.) and the pale brown solid was filtered off. This was recrystallised from acetone twice to give octachloro-6-diethylaminophenanthridine. (Yield = 0·4g., 19%). M.p. 131-132°C. (Found: C, 39·0; N, 5·1; H, 1·2; Cl, 54·2%. $C_{17}N_2H_{10}Cl_8$ requires C, 38·82; N, 5·33; H, 1·92; Cl, 53·93%). Molecular weight = 522 with eight chlorine atoms. Infra-red spectrum No. 10. N.M.R. spectrum No. 2.

(iii) t-Butylamine. Nonachlorophenanthridine (0·5g.) was stirred with refluxing t-butylamine (50 ml.) for 24 h. The resulting mixture was added to water (100 ml.) and the solid was filtered off. This was a mixture of starting material, octachlorophenanthridines and substitution products.

(Identified by the mass spectrum. Parent peaks at 485 with nine chlorine atoms, 451 with eight chlorine atoms and 520 with eight chlorine atoms).

(iv) Thiophenoxide Ion. Sodium (0·06g., 2·61 mmole) was added to dry, stirred methanol (100 ml.) and then thiophenol (2 ml.) was added, followed by nonachlorophenanthridine (1·00g., 2·04 mmole), and the mixture was refluxed for $1\frac{1}{2}$ h. Water (50 ml.) was added and the resulting solid was filtered off. This was a mixture of octachlorophenanthridines. (Identified by the mass spectrum. Parent peak at 451 with eight chlorine atoms).

3.4 Reactions with Organometallic Reagents

The procedure for standardising the n-butyl lithium solution was as follows. Samples of the solution of n-butyl lithium in n-hexane (1 ml.) were added to water (20 ml.), and the resulting mixture was titrated against 0·1N sulphuric acid, using phenolphthalein as indicator. This was carried out on three samples, and the most consistent titre was used to calculate the total lithium content of the solution. Other samples of the solution of n-butyl lithium (1 ml.) were added to redistilled benzyl chloride (1 ml.) in dry ether (15 ml.). Water (10 ml.) was added after $\frac{1}{2}$ h., and the resulting mixture was titrated as before. This procedure, too, was carried out on three samples, and the most consistent titre was used to calculate the non-organometallic lithium content of the solution.

In all of these reactions, the apparatus was rinsed with acetone and thoroughly dried in an oven before use.

A. Nonachloroacridine

(i) Reactions with n-Butyl Lithium. In the reactions where only starting material was recovered, nonachloroacridine (2·0g., 4·1 mmole) and dry ether (150 ml.) were placed in a flask fitted with magnetic stirrer, gas inlet, dropping funnel and condenser, which was continuously purged with dry nitrogen gas, before and during the experiment. The mixture was cooled

to 0°C and a 2·0M solution of n-butyl lithium in n-hexane (3 ml., 6 mmole) was slowly added, while the mixture was stirred. Stirring was continued at this temperature for 2½ h., and then for another 2 h. at room temperature. N-Hydrochloric acid (10 ml.) was then added and the resultant was stirred for a final 2 h. The solid that was filtered off was unchanged nonachloroacridine. (Identified by a comparison of its infra-red spectrum with that of an authentic sample from 2.2.A).

In the reactions which produced octachloroacridine, nonachloroacridine and dry ether were placed in the flask as before, but they were cooled to -78°C. An approximately 2M solution of n-butyl lithium in n-hexane (3 ml., 6 mmole) was slowly added and stirring was carried out at -78°C for 4 h. N-Hydrochloric acid (10 ml.) was then added and stirring was continued while the mixture was allowed to warm to room temperature. The solid which was filtered off was recrystallised from chloroform, to give off-white crystals of 1,2,3,4,5,6,7,8-octachloroacridine. (Yield = 1·1g., 59%). M.p. 167-168°C. (Found: Cl, 62·1%. $C_{13}NHCl_8$ requires Cl, 62·44%. This experiment could not be repeated, and there was not enough material left to obtain a carbon analysis). Molecular weight = 451 with eight chlorine atoms. Infra-red spectrum No. 11.

Part of this octachloroacridine (0·8g.) was refluxed with water (25 ml.) and concentrated hydrochloric acid (25 ml.) for 24 h. The solid produced was unchanged octachloroacridine. (Identified by its infra-red spectrum).

In the reaction which produced 9-n-butyl-1,2,3,4,5,6,7,8-octachloroacridan, nonachloroacridine and dry ether were placed in the flask as before and cooled to -78°C. A 0·2M solution of n-butyl lithium in n-hexane (5 ml., 1·0 mmole) was added and the mixture was stirred at -78°C for 3 h. N-Hydrochloric acid (20 ml.) was then added and stirring was continued while the mixture was allowed to warm to room temperature. The solid was filtered off and sublimed under 0·003 mm. Hg. at 120°C., giving yellow 9-n-butyl-

1,2,3,4,5,6,7,8-octachloroacridan. (Yield = 0·2g., 10%). M.p. 139-141°C. (Found: C, 39·6; H, 2·31; Cl, 55·4%. $C_{17}NH_{11}Cl_8$ requires C, 39·81; H, 2·16; Cl, 55·30%). The mass spectrum gave no parent peak. Infra-red spectrum No. 12. N.M.R. spectrum No. 3.

(ii) Reaction with Phenyl Magnesium Bromide. Both before and during this reaction the apparatus was continuously purged with dry nitrogen gas. Magnesium (1·0g., 41·6 mmole) and dry ether (100 ml.) were placed in a flask fitted with a magnetic stirrer, condenser, dropping funnel and gas inlet. A solution of bromobenzene (6·5g., 41·5 mmole) in dry ether (50 ml.) was added at such a rate as to maintain a steady reflux. After addition was complete, stirring and refluxing were continued for $\frac{1}{2}$ h. Nonachloroacridine (2·0g., 4·1 mmole) was then added, and stirring and refluxing were continued for another 2 h. Dilute hydrochloric acid was added to the cooled mixture produced until effervescence had ceased, and the solid was filtered off. This was unchanged nonachloroacridine. (Identified by a comparison of its infra-red spectrum with that of an authentic sample from 2.2.A).

B. Reaction of Nonachlorophenanthridine with n-Butyl Lithium

The apparatus was continually purged with dry nitrogen gas, both before and during this reaction. Nonachlorophenanthridine (2·0g., 4·1 mmole) and dry ether (150 ml.) were placed in a flask fitted with a magnetic stirrer, gas-tap, condenser and dropping funnel. A 2·0M solution of n-butyl lithium in n-hexane (3 ml., 6·0 mmole) was added and the mixture was stirred and refluxed for 3 h. After cooling to room temperature, N-hydrochloric acid (10 ml.) was cautiously added and stirring was continued overnight. The resulting solid was filtered off, and was unchanged nonachlorophenanthridine. (Identified by a comparison of its infra-red spectrum with that of an authentic sample from 2.2.B).

3.5 Oxidation and Reduction Reactions

A. Nonachloroacridine

(i) Oxidation. Nonachloroacridine (1·0g., 2·0 mmole), glacial acetic acid (20 ml.) and concentrated sulphuric acid (25 ml.) were stirred together and cooled to 0°C. A 90% solution of hydrogen peroxide (2 ml., 53 mmole) was slowly added with vigorous stirring. Stirring was continued at 0°C for 1 h. and then at room temperature for 48 h. The resulting mixture was poured onto ice-water (200 ml.), which was vigorously stirred. The green solid, filtered off, was octachloro-9-acridanone. (Identified by a comparison of its infra-red spectrum with that of an authentic sample from 3.2.A.(i)).

(ii) Reduction with Lithium Aluminium Hydride. Nonachloroacridine (1·0g., 2·0 mmole) and dry ether (150 ml.) were cooled to 0°C, and stirred in a flask which had been well dried and was continuously purged with dry nitrogen gas. Lithium aluminium hydride (0·5g., 13·1 mmole) was added and stirring was continued at 0°C for 2 h. The resultant mixture was allowed to stand overnight, and then a mixture of water (5 ml.) and concentrated sulphuric acid (5 ml.) was added very slowly and cautiously. The green solid produced was filtered off. This was a complex mixture, chiefly containing quite extensively reduced acridines and acridans. (Identified by the mass spectrum. Parent peaks at 487 with nine chlorine atoms, 451 with eight chlorine atoms, and so on).

(iii) Reduction with Sodium Borohydride. Nonachloroacridine (2·0g., 4·1 mmole) and sodium borohydride (1·0g., 26·3 mmole) were refluxed in dry ether (150 ml.) for 1½ h. The yellow solid produced was filtered off, and it was unchanged nonachloroacridine. (Identified by a comparison of its infra-red spectrum with that of an authentic sample from 2.2.A).

B. Oxidation of Octachloro-9-acridanone

Octachloro-9-acridanone (2·0g., 4·3 mmole) and glacial acetic acid (50 ml.) were stirred together. A solution of potassium dichromate (2·0g., 8·1 mmole) in glacial acetic acid (150 ml.) was slowly added, and the resulting mixture was refluxed for $1\frac{1}{2}$ h. The resultant was cooled, added to water (300 ml.) and the solid was filtered off. This was unchanged octachloro-9-acridanone. (Identified by a comparison of its infra-red spectrum with that of an authentic sample from 3.2.A.(i)).

3.6 Pyrolysis and Photolysis Reactions

A. Photolysis of Nonachloroacridine in Methanol

Nonachloroacridine (1·0g.) and dry methanol (20 ml.) were placed in a pyrex Carius tube, which was evacuated and then let down to an atmosphere of dry nitrogen gas several times, to de-gas the solvent. Finally, the tube was evacuated and sealed. It was then irradiated with ultra-violet light (500 watt, medium-pressure mercury lamp) for 66 h.

The tube was then cooled, opened, and the contents washed out with methanol. The solid which was filtered off was unchanged nonachloroacridine. (Identified by a comparison of its infra-red spectrum with that of an authentic sample from 2.2.A).

B. Pyrolysis of Octachloro-9-acridanone

(i) Under Atmospheric Pressure. Octachloro-9-acridanone (0·5g.) was heated at 260°C for 18 h. in a test tube, while a gentle stream of dry nitrogen gas was passed slowly into the tube. The resulting solid was recrystallised from chlorobenzene and gave unchanged octachloro-9-acridanone. (Identified by a comparison of its infra-red spectrum with that of an authentic sample from 3.2.A.(i)).

(ii) In an Autoclave. Octachloro-9-acridanone (5g.) was sealed in an autoclave, which was evacuated, heated at 400°C for 5 h., and then allowed to cool. Volatiles, which were all gaseous at room temperature, were transferred out, under vacuum into a cold trap.

The autoclave was then let down to an atmosphere of dry nitrogen gas, opened, and the residue was recrystallised from chlorobenzene to give a degraded orange solid.

C. Photolysis of Octachloro-9-acridanone

(i) In an Inert Solvent. Octachloro-9-acridanone (0·2g.) was dissolved in dry benzene (200 ml.) and the solution was placed in a silica tube, fitted with a gas bubbler. The tube was irradiated with light from a 300 nm lamp for 60 h. The solvent was then removed from the mixture to leave unchanged octachloro-9-acridanone. (Identified by a comparison of its infra-red spectrum with that of an authentic sample from 3.2.A.(i)).

(ii) In Isopropanol. Octachloro-9-acridanone (2·0g.) and isopropanol (40 ml.) were sealed in a pyrex Carius tube, which was evacuated and then irradiated with ultra-violet light (500 watt, medium-pressure mercury lamp) for 17 h. The tube was then cooled, opened, and the solid was filtered off. This was unchanged octachloro-9-acridanone. (Identified by a comparison of its infra-red spectrum with that of an authentic sample from 3.2.A.(i)).

D. Pyrolysis of Nonachlorophenanthridine

Nonachlorophenanthridine (0·5g.) was passed, under vacuum, through a silica tube heated to 800°C, and the product was collected in a cold trap. The orange solid produced was tentatively identified as nonachlorobiphenyl-2-cyanide. Molecular weight = 485 with nine chlorine atoms. Infra-red spectrum No. 13, shows weak nitrilic absorbtions.

An attempt was made to hydrolyse the product. It was stirred with water (5 ml.) and concentrated sulphuric acid (15 ml.) at 80°C for 16 h.

The solid was filtered off and washed well with water. The identity of this solid was uncertain.

4. Experimental for Chapter IV - Nucleophilic Substitutions in Heptachloroquinoline and Heptachloroisoquinoline:- The use of ^{13}C N.M.R. in Assignment of Orientation

4.1 Reactions with Simple Nucleophiles

A. Heptachloroquinoline

(i) One Equivalent of Methoxide Ion. Sodium (0·06g., 2·60 mmole) was dissolved in dry methanol (5 ml.) and this solution was added to a suspension of heptachloroquinoline (1·00g., 2·70 mmole) in dry methanol (25 ml.). This mixture was stirred at room temperature for 2 h., then poured onto water (50 ml.) and the solid was filtered off.

Thin layer chromatography, using petroleum 40-60° as eluant, showed that there were four components in this solid, one of which had the same R_f value as heptachloroquinoline, and another of which was only present in very small amounts. Samples of each of the three major components were obtained by separation by column chromatography using silica (Silic AR CC-7, 100-200 mesh; Mallinckrodt Chemical Works) as solid phase in a 40 cm x 3 cm^2 column, and petroleum 40-60° as eluant. The component with the same R_f value as heptachloroquinoline was, indeed heptachloroquinoline. (Identified by a comparison of its infra-red spectrum with that of the starting material). One other component was pentachlorodimethoxyquinoline. (Identified by a comparison of its infra-red spectrum with that of an authentic sample from 4.1.A.(ii)).

The third component was recrystallised from acetone, to give a hexachloromethoxyquinoline (probably hexachloro-2-methoxyquinoline). (Yield = 0·15g., 15%). M.p. 198-199°C. (Found: C, 32·5; N, 3·4; H, 1·2; Cl, 58·1%. $C_{10}NH_3OCl_6$ requires C, 32·82; N, 3·84; H, 0·83; Cl, 58·01%).

Molecular weight = 363 with six chlorine atoms. Infra-red spectrum No. 14. N.M.R. spectrum No. 4.

(ii) Two Equivalents of Methoxide Ion. Sodium (0·12g., 5·20 mmole) was dissolved in dry methanol (5 ml.), and this solution was added to a suspension of heptachloroquinoline (1·00g., 2·70 mmole) in dry methanol (40 ml.). The mixture was refluxed for 24 h., added to water (50 ml.) and the solid was filtered off. Thin layer chromatography, using petroleum 40-60° as eluant, showed one major component, with the same R_f value as one of the components from the reaction with one equivalent of methoxide ion. This was purified by column chromatography, using conditions as in (i), but with the column 20 cm. long, and by recrystallisation from acetone, to give pure pentachloro-dimethoxyquinoline (probably pentachloro-2,4-dimethoxyquinoline). (Yield = 0·28g., 28%). M.p. 192-193°C. (Found: C, 36·6; N, 3·6; H, 2·0%. $C_{11}NH_6O_2Cl_5$ requires C, 36·55; H, 3·88; H, 1·67%). Molecular weight = 359 with five chlorine atoms. Infra-red spectrum No. 15. N.M.R. spectrum No. 5.

(iii) Diethylamine. Heptachloroquinoline (1·0g.) was refluxed with diethylamine (40 ml.) for 24 h. The excess diethylamine was then removed from the product and the resulting solid, which was shown by thin layer chromatography, using petroleum 40-60° as eluant, to be almost one component only, was recrystallised from acetone to give yellow crystals of hexachloro-2-diethylaminoquinoline. (Yield = 0·5g., 45%). M.p. 77-78°C. (Found: C, 38·5; N, 6·7; H, 2·7; Cl, 52·8%. $C_{13}N_2H_{10}Cl_6$ requires C, 38·37; N, 6·68; H, 2·48; Cl, 52·27%). Molecular weight = 404 with six chlorine atoms. Infra-red spectrum No. 16. N.M.R. spectra Nos. 6 and 7.

B. Heptachloroisoquinoline

(i) Methoxide Ion. Sodium (0·06g., 2·60 mmole) was dissolved in dry methanol (5 ml.), and the solution was added to a suspension of heptachloro-

isoquinoline (1·00g., 2·70 mmole) in dry methanol (40 ml.). The resulting mixture was stirred and refluxed for 16 h. The solid that was filtered off was shown to be essentially a single component, by thin layer chromatography, using petroleum 40-60° as eluant. This solid was recrystallised from acetone to give hexachloro-1-methoxyisoquinoline. (Yield = 0·16g., 16%). M.p. 158-160°C. (Found: C, 32·9; N, 3·8; H, 0·9; Cl, 57·5%. $C_{10}NH_3OCl_6$ requires C, 32·82; N, 3·83; H, 0·83; Cl, 58·01%). Molecular weight = 363 with six chlorine atoms. Infra-red spectrum No. 17. N.M.R. spectra Nos. 8 and 9.

In an attempt to obtain disubstitution, sodium (0·12g., 5·20 mmole) was dissolved in dry methanol (5 ml.) and the solution was added to a suspension of heptachloroisoquinoline (1·00g., 2·70 mmole) in dry methanol (40 ml.). The resulting mixture was stirred and refluxed for a week, and then the solid was filtered off. This was hexachloro-1-methoxyisoquinoline. (Identified by a comparison of its infra-red spectrum with that of the sample obtained above).

(ii) Diethylamine. Heptachloroisoquinoline (0·9g., 2·5 mmole) was stirred and refluxed with diethylamine (50 ml.) for 24 h. Thin layer chromatography, using petroleum 40-60° as eluant, showed that the material filtered off was essentially one component. This was recrystallised from acetone to give yellow crystals of hexachlorodiethylaminoisoquinoline (probably hexachloro-1-diethylaminoisoquinoline). (Yield = 0·3g., 27%). M.p. 116-118°C. (Found: C, 38·6; N, 7·1; H, 2·8; Cl, 51·9%. $C_{13}N_2H_{10}Cl_6$ requires C, 38·37; N, 6·68; H, 2·48; Cl, 52·27%). Molecular weight = 404 with six chlorine atoms. Infra-red spectrum No. 18. N.M.R. spectrum No. 10.

4.2 Reactions of Heptachloroquinoline with Sulphur Nucleophiles

In the reaction with sodium disulphide, a solution of sodium disulphide was prepared by adding hydrated sodium sulphide (3·1g., 12·9 mmole) and then

sulphur (0·4g., 12·5 mmole) to refluxing ethanol (15 ml.). This solution was added, while warm, to a refluxing suspension of heptachloroquinoline (3·0g., 8·2 mmole) in ethanol (100 ml.) over 2 h., and then refluxing was continued for 3 h., while the mixture was stirred.

After cooling, the solid was filtered off and washed well with water; this was unchanged heptachloroquinoline. (Identified by a comparison of its infra-red spectrum with that of the starting material).

In the reaction with elemental sulphur, heptachloroquinoline (2·0g., 5·5 mmole) and sulphur (2·0g., 65 mmole) were well mixed, and heated at 320°C for ½ h. in a test tube, while a gentle stream of dry nitrogen gas was passed into the tube. After cooling, excess sulphur was removed by sublimation under vacuum, and the residue was recrystallised from chlorobenzene to give pale orange crystals of 2,3,6,7,8-pentachloroquino-[4,5-cd]-1,2-dithiole. (Yield = 0·8g., 41%). M.p. 156-158°C. (Found: C, 29·3%. $C_9NS_2Cl_5$ requires C, 29·74%. In general analysis was poor because of under oxidation (in the case of CHN) and because of interference between sulphur and chlorine). Molecular weight = 361 with five chlorine atoms. Infra-red spectrum No. 19.

4.3 Reaction of Heptachloroquinoline with n-Butyl Lithium

Before use, all the apparatus was rinsed with acetone and thoroughly dried in an oven. Both before and during the reaction, the apparatus was continually purged with dry nitrogen gas. Heptachloroquinoline (1·0g., 2·7 mmole) and dry ether (100 ml.) were placed in a flask fitted with magnetic stirrer, gas inlet, condenser and dropping funnel. The flask was cooled to -78°C, and the contents were stirred. A 2·0M solution of n-butyl lithium in n-hexane (2 ml., 4·0 mmole) was slowly added, and stirring was continued at -78°C for 3 h. N-Hydrochloric acid (10 ml.) was then slowly added, and stirring was continued while the mixture was allowed to warm to room temperature.

The ether layer was separated from the resulting mixture, and the solvent was removed to leave a brown oil. Thin layer chromatography using petroleum 40-60° as eluant, showed this to be a very complex mixture.

4.4 Reactions of Octachloronaphthalene

A. Methoxide Ion

Sodium (0·1g., 4·4 mmole) was dissolved in dry methanol (15 ml.) and this solution was sealed in a nickel tube with octachloronaphthalene (2·0g., 4·9 mmole). The tube was rotated in an oil bath at 200°C for 24 h. It was then cooled, opened, and the contents were washed out with methanol. The solid which was filtered off was unchanged octachloronaphthalene. (Identified by a comparison of its infra-red spectrum with that of the starting material).

B. Amines

(i) Diethylamine in Sulpholane. Octachloronaphthalene (4·0g., 9·9 mmole), diethylamine (1·0g., 14·9 mmole) and dry sulpholane (30 ml.) were stirred together at 120°C for 40 h. The resulting solution was cooled and mixed with water (300 ml.). The solid which was filtered off was unchanged octachloronaphthalene. (Identified by a comparison of its infra-red spectrum with that of the starting material).

(ii) Excess Diethylamine. Octachloronaphthalene (1·0g., 2·5 mmole) was stirred with refluxing diethylamine (60 ml.) for 120 h. The resulting mixture was cooled and added to water (100 ml.). A grey solid was filtered off which was a mixture of chlorohydronaphthalenes. (Identified by the mass spectrum. Parent peaks at 366 with seven chlorine atoms, 332 with six chlorine atoms, and so on).

(iii) t-Butylamine. Octachloronaphthalene (2·0g., 4·9 mmole) was sealed with t-butylamine (30 ml.) in a nickel tube, and the tube was rotated in an oil bath at 80°C for 15 h. It was then cooled, opened, and the

contents were washed out with methanol. The solid filtered off was a mixture of chlorohydronaphthalenes and starting material. (Identified by the mass spectrum. Parent peaks at 400 with eight chlorine atoms, 366 with seven chlorine atoms, and so on).

(iv) Ammonia. Octachloronaphthalene (2·0g.), ·880d ammonia solution (10 ml.) and ethanol (20 ml.) were sealed together in a nickel tube which was rotated in an oil bath at 160°C for 24 h. The tube was cooled, opened, and the contents were washed out with ethanol. The solid that was filtered off was a mixture of mostly heptachloronaphthalene and aminohexachloronaphthalene. (Identified by the mass spectrum. Parent peaks at 366 with seven chlorine atoms, and 347 with six chlorine atoms).

This material was recrystallised from chloroform and sublimed under 0·01 mm. Hg. at 100°C to give grey aminohexachloronaphthalene. (Yield = 0·6g., 35%). M.p. 201-203°C. (Found: C, 34·1; Cl, 61·1%. $C_{10}NH_3Cl_6$ requires C, 34·33; Cl, 60·80%). Molecular weight = 347 with six chlorine atoms. Infra-red spectrum No. 20.

C. Lithium Diethylamide

All the apparatus was rinsed with acetone and dried thoroughly in an oven before use. Both before and during the reaction, the apparatus was continually purged with dry nitrogen gas. Diethylamine (1·0g., 14·9 mmole) and dry ether (20 ml.) were stirred and cooled to -78°C, in a flask fitted with a condenser, dropping funnel, and gas inlet. A 2·0M solution of n-butyl lithium in n-hexane (8 ml., 16·0 mmole) was slowly added, and the resulting mixture was stirred at -78°C for 2 h. Octachloronaphthalene (5·0g., 12·4 mmole) in dry ether (150 ml.) was precooled to -78°C, and then slowly added. Stirring was continued at this temperature for 3 h., and then the mixture was allowed to warm to -30°C. 2N Hydrochloric acid (25 ml.) was then slowly added and stirring was continued while the mixture was allowed to warm to room temperature.

The solid, which was obtained by filtration of the resultant, was unchanged octachloronaphthalene. (Identified by a comparison of its infra-red spectrum with that of the starting material. Recovery 5%).

The solvent was removed from the ether layer to give a black tar which had broad absorbtions in the infra-red spectrum and was not investigated any further.

5. Experimental for Chapter V - Perfluoro-5,6,7,8-tetrahydro-quinoline and -isoquinoline:- The Mechanism of Their Formation and Some of Their Properties

5.1 Mechanistic Investigations

A. Preparation of Starting Materials

(i) 5,6,7,8-Tetrachloroheptafluoroquinoline. Heptafluoroquinoline (5·0g., 19·6 mmole) was placed in a pyrex Carius tube and chlorine gas (1 litre, 44·7 mmole) was transferred into the tube under vacuum. The tube was then sealed under vacuum and irradiated with ultra-violet light (500 watt, medium-pressure mercury lamp) for 48 h.

The tube was cooled and opened, and the contents were washed out with, and dissolved in, ether (200 ml.). The ether solution was dried with anhydrous magnesium sulphate, filtered, and the solvent removed from the filtrate to leave a yellow oil. Pure 5,6,7,8-tetrachloroheptafluoroquinoline, a viscous yellow liquid, was obtained (by sublimation under 0·005 mm. Hg. at 100°C). (Yield = 5·3g., 69%). Purity was demonstrated by vapour phase chromatography at 250°C. (Identified by a comparison of its infra-red spectrum with that of a previously reported sample[222]).

(ii) 5,6,7,8-Tetrachloroheptafluoroisoquinoline. Heptafluorisoquinoline (5·0g., 19·6 mmole) was placed in a pyrex Carius tube and chlorine gas (1 litre, 44·7 mmole) was transferred into the tube under vacuum. The tube was then sealed under vacuum and irradiated with ultra-violet light (500 watt, medium-

pressure mercury lamp) for 96 h. The tube was then cooled and opened, and the contents were washed out with, and dissolved in, ether (200 ml.). The ether was dried with anhydrous magnesium sulphate and then filtered; the solvent was removed from the filtrate and sublimation of the residue under 0·005 mm. Hg. at 100°C gave 5,6,7,8-tetrachloroheptafluoroisoquinoline, a viscous yellow liquid. (Yield = 4·6g., 60%). B.p. > 200°C. (Found: C, 28·0; F, 33·0%. $C_9NF_7Cl_4$ requires C, 27·23; F, 33·47%). Molecular weight = 395 with four chlorine atoms. Infra-red spectrum No. 21. N.M.R. spectrum No. 11. Vapour phase chromatography at 250°C showed one component.

B. Fluorination at Atmospheric Pressure

(i) 5,6,7,8-Tetrachloroheptafluoroquinoline. The fluorinating agent used was caesium fluoride doped with sulpholane. This was prepared by placing dry caesium fluoride (10g.) and dry sulpholane (20 ml.) in one arm of a dry Schlenk tube which was purged with dry nitrogen. These reagents were stirred together and then filtered through the sinter. More of the sulpholane was removed from the solid by heating under vacuum, and this gave sulpholane doped caesium fluoride.

All the apparatus was rinsed with acetone and thoroughly dried in an oven before use. 5,6,7,8-Tetrachloroheptafluoroquinoline (3·5g., 8·9 mmole) and sulpholane doped caesium fluoride (10g., ~65 mmole) were placed in a conical flask fitted with a magnetic stirrer, gas-tap, and variable volume reservoir to allow for expansion. The flask was evacuated and let down to an atmosphere of dry nitrogen gas, and then the contents were stirred at 160°C for 24 h.

After cooling, the residue was mixed with water (200 ml.) and chloroform (200 ml.), and the chloroform layer was separated. The aqueous layer was re-extracted with chloroform (2 x 100 ml.), and the combined chloroform layers were washed with water (3 x 200 ml.) and dried over anhydrous magnesium sulphate. After filtering, the solvent was removed from the

filtrate to leave a brown oil, from which perfluoro-5,6,7,8-tetrahydroquinoline was obtained as a clear liquid by vacuum transfer. (Yield = 0·3g., 10%). (Identified by a comparison of its infra-red spectrum with that of the sample obtained earlier[222]).

(ii) 5,6,7,8-Tetrachloroheptafluoroisoquinoline. This fluorination was also achieved with sulpholane doped caesium fluoride as the reagent, and it was prepared as described in (i) above.

All the apparatus was rinsed with acetone and thoroughly dried in an oven before use. 5,6,7,8-Tetrachloroheptafluoroisoquinoline (4·0g., 10·1 mmole) and sulpholane doped caesium fluoride (10g., ~65 mmole) were placed in a conical flask fitted with a magnetic stirrer, gas-tap and variable volume reservoir to allow for expansion. The apparatus was evacuated, let down to an atmosphere of dry nitrogen gas, and then the contents were stirred at 160°C for 24 h. After cooling, the residue was mixed with chloroform (200 ml.) and water (200 ml.). The organic layer was separated, and the aqueous layer was extracted with more chloroform (2 x 100 ml.). The combined chloroform layers were washed thoroughly with water (3 x 200 ml.) and dried with anhydrous magnesium sulphate. After filtering, the solvent was removed from the filtrate to leave a brown oil, which was shown by vapour phase chromatography at 150°C to consist of essentially two components. These were separated by preparative scale vapour phase chromatography at 160°C. The more volatile of the two components was perfluoro-5,6,7,8-tetrahydroisoquinoline. (Yield = 0·7g., 21%). (Identified by a comparison of its infra-red spectrum with that of a sample obtained earlier[210]). Infra-red spectrum No. 22.

C. 1,2,3,4,5,6-Hexachlorohexafluorocyclohexane

(i) Preparation. Hexafluorobenzene (5·0g., 26·9 mmole) was placed in a pyrex Carius tube and chlorine gas (2 litres, 89·4 mmole) was transferred into the tube under vacuum. The tube was then sealed under vacuum and

irradiated with ultra-violet light (500 watt, medium-pressure mercury lamp) for 48 h.

The tube was then cooled and opened, and the contents were dissolved in ether (200 ml.). The ether solution was washed with aqueous sodium metabisulphite solution (2 x 100 ml.) and then dried with phosphorus pentoxide. After filtering, the solvent was removed from the filtrate to leave a solid which was distilled under the reduced pressure of a water pump at 110°C, to give 1,2,3,4,5,6-hexachlorohexafluorocyclohexane, a waxy white solid. (Yield = 3·6g., 35%). M.p. 100-102°C; literature value 101-102°C.[215]

(ii) Reaction with Sulpholane Doped Caesium Fluoride. The doped caesium fluoride was prepared as in 5.1.B.(i) above. The apparatus was all rinsed with acetone and thoroughly dried in an oven before use. 1,2,3,4,5,6-Hexachlorohexafluorocyclohexane (3·0g., 7·6 mmole) and sulpholane doped caesium fluoride (4·5g., ~30mmole) were placed in a conical flask fitted with a magnetic stirrer, gas-tap and variable volume reservoir to allow for expansion. The flask was evacuated, let down to an atmosphere of dry nitrogen gas, and then the contents were stirred at 160°C for 24 h.

After cooling, the residue was mixed with dichloromethane (200 ml.) and water (200 ml.), and the organic layer was separated. The aqueous layer was extracted with more dichloromethane (2 x 100 ml.), and the combined organic layers were washed with water (3 x 200 ml.), and dried with anhydrous magnesium sulphate. After filtering, the solvent was removed from the filtrate and left unchanged 1,2,3,4,5,6-hexachlorohexafluorocyclohexane. (Identified by a comparison of its infra-red spectrum with that of the starting material).

5.2 Reactions of Perfluoro-5,6,7,8-tetrahydroisoquinoline

A. Fluorination with Cobalt Trifluoride

The fluorination was carried out in a tube containing cobalt fluorides, which were stirred by the rotation of a paddle-screw that passed along the length of the tube. The cobalt fluorides were initially all converted to cobalt trifluoride by the passage of fluorine gas, for $1\frac{1}{2}$ h., through the tube which was heated to 280°C, from a fluorine generator operating at 10 amps.

The tube was then purged with dry nitrogen gas and allowed to cool to 120°C. Perfluoro-5,6,7,8-tetrahydroisoquinoline (3·0g.) was then dripped into the beginning of the tube and carried along it by a dry nitrogen gas flow of 200 ml.m^{-1}. The products were collected in a cold trap for a total of 2 h. after the passage of reactant through the tube was begun. (Recovery = 1·6g., 53%).

Vapour phase chromatography at 78°C showed that this product was a complex mixture of seven components. Combined gas chromatography/mass spectrometry gave the molecular weights of these components as 331, 331, 407, 350, 388, 426 and 449. These probably corresponded to the molecular formulae C_9NF_{11}, C_9NF_{11}, C_9NF_{15}, C_7F_{14}, C_7F_{16}, C_7F_{18} and C_9NF_{17}.

B. Reactions with Methoxide Ion

(i) One Equivalent of Methoxide Ion. Perfluoro-5,6,7,8-tetrahydroisoquinoline (1·00g., 3·02 mmole) was stirred with dry methanol (30 ml.) and sodium (0·07g., 3·04 mmole) was added. Stirring was continued at room temperature for 2 h. The methanol was then removed, and the residue was mixed with water (50 ml.) and cyclohexane (50 ml.). The organic layer was separated and dried with anhydrous magnesium sulphate. After filtering, the solvent was removed from the filtrate and the resulting yellow solid was sublimed at 70°C, under 0·005 mm Hg., to give white 3-methoxyperfluoro-5,6,7,8-tetrahydroisoquinoline. (Yield = 0·65g., 63%). M.p. 42-43°C.

(Found: C, 35·1; H, 1·3%. $C_{10}NH_3OF_{10}$ requires C, 35·00; H, 0·88%). Molecular weight = 343. Infra-red spectrum No. 23. N.M.R. spectra Nos. 12 and 13. Vapour phase chromatography gave one component at 240°C.

(ii) Two Equivalents of Methoxide Ion. Perfluoro-5,6,7,8-tetrahydroisoquinoline (1·00g., 3·02 mmole) was stirred with dry methanol (30 ml.) and sodium (0·15g., 6·53 mmole) was added. The resulting mixture was refluxed for 18 h. and then the solvent was removed. The residue was shaken with water (50 ml.) and cyclohexane (50 ml.), and the organic layer was separated and dried with anhydrous magnesium sulphate. After filtering, the solvent was removed from the filtrate to leave a yellow solid, which was shown by vapour phase chromatography at 240°C to be a mixture of two components. The most volatile, minor, component had the same retention time as 3-methoxyperfluoro-5,6,7,8-tetrahydroisoquinoline.

The major, less volatile component was separated by preparative scale vapour phase chromatography at 250°C. This was white 1,3-dimethoxyperfluoro-5,6,7,8-tetrahydroisoquinoline. (Yield = 0·35g., 33%). M.p. 56-57°C. (Found: C, 37·2; N, 4·3; H, 1·5%. $C_{11}NH_6O_2F_9$ requires C, 37·20; N, 3·94; H, 1·70%). Molecular weight = 355. Infra-red spectrum No. 24. N.M.R. spectra Nos. 14 and 15.

C. Reaction with Diethylamine

Perfluoro-5,6,7,8-tetrahydroisoquinoline (2·00g., 6·04 mmole) was stirred with ethanol (30 ml.) and diethylamine (0·44g., 6·03 mmole) was added. The resulting mixture was stirred at room temperature for 18 h., and then the solvent was removed, leaving a yellow oil. This was shaken with water (50 ml.) and cyclohexane (50 ml.), and the organic layer was separated and dried with anhydrous magnesium sulphate. After filtering, the solvent was removed from the filtrate to leave a yellow oil, which was sublimed at 70°C under 0·005 mm. Hg. The vapour phase chromatograph at

250°C showed that two components were present in the resulting material.

Preparative scale vapour phase chromatography at 250°C, gave 3-diethylaminoperfluoro-5,6,7,8-tetrahydroisoquinoline, the less volatile component, as a yellow liquid. (Yield = 0·46g., 20%). B.p. > 200°C. (Found: C, 40·2; N, 6·8%. $C_{13}N_2H_{10}F_{10}$ requires C, 40·64; N, 7·29%). Molecular weight = 384. Infra-red spectrum No. 25. N.M.R. spectra Nos. 16 and 17.

D. Reaction with Hexafluoropropene in the Presence of Fluoride Ion

All the apparatus was rinsed with acetone and thoroughly dried in an oven before use. Perfluoro-5,6,7,8-tetrahydroisoquinoline (2·0g., 6·1 mmole) dry caesium fluoride (5·0g., 32·0 mmole) and dry sulpholane (20 ml.) were stirred together in a conical flask, fitted with a gas-tap and variable volume reservoir. The apparatus was evacuated and then filled with hexafluoropropene (13·0g., 86·6 mmole). The resulting mixture was stirred at room temperature for $2\frac{1}{2}$ h., by which time all the gas had been used up. Volatiles were then transferred out of the reaction mixture, under vacuum, into a cold trap. The material obtained was perfluoro-5,6,7,8-tetrahydro-1,3-bisisopropylisoquinoline, a colourless liquid. (Yield = 1·6g., 42%). B.p. 122°C. (Micro-analysis gave inconsistent results, probably because of loss of fluorinated olefin from the side chains without oxidation). Molecular weight = 631. Infra-red spectrum No. 26. N.M.R. spectrum No. 18. Vapour phase chromatography at 150°C and 250°C showed one component.

E. Reactions with Hydrazine

The unstable hydrazino derivative was prepared in the following way. Perfluoro-5,6,7,8-tetrahydroisoquinoline (2·0g., 6·1 mmole) was stirred with ethanol (50 ml.) at 0°C, and a 60% solution of hydrazine hydrate (1·0g., 12 mmole) was added. Stirring was continued at 0°C for 2 h., the solid was filtered off and the solvent was removed from the filtrate to leave a tarry brown material. From its further reactions, this material seemed to

contain 3-hydrazino-perfluoro-5,6,7,8-tetrahydroisoquinoline.

The impure bromo derivative was prepared as follows. The residue of hydrazino compound was added, over half an hour, to a stirred solution of cupric bromide (8·0g.) in 50% hydrobromic acid (30 ml.), at room temperature. Stirring was continued for another half hour and then the residue was mixed with water (100 ml.) and ether (150 ml.). The ether layer was separated, and the aqueous layer re-extracted with ether (100 ml.). The combined ether layers were dried over anhydrous magnesium sulphate and then filtered. The solvent was removed from the filtrate, leaving a brown oil, which was sublimed under 0·005 mm. Hg. at 50°C to give an orange solid. This was impure 3-bromoperfluoro-5,6,7,8-tetrahydroisoquinoline. (Yield = 0·2g., 8%). Molecular weight = 391 (Br = 79) with one bromine atom. Infra-red spectrum No. 27. N.M.R. spectrum No. 19. Vapour phase chromatography at 150°C, appeared to show only one component.

The impure hydro derivative was prepared as follows. The residue of hydrazino compound was stirred with water (50 ml.) at room temperature and a solution of copper sulphate (3·0g.) in water (50 ml.) was added over $1\frac{1}{2}$ h. Stirring was then continued for another 2 h. Water (50 ml.) and ether (150 ml.) were added and the ether layer was separated. The aqueous layer was extracted with more ether (100 ml.) and the combined ether layers were dried with anhydrous magnesium sulphate. After filtering, the solvent was removed from the filtrate and left a black solid. Sublimation under 0·005 mm. Hg. at up to 150°C produced a very small amount ($< 0·1$g.) of a yellow solid, which slowly darkened and contained some monohydroperfluoro-5,6,7,8-tetrahydroisoquinoline. (Identified by the mass spectrum. Parent peak at 313).

5.3 Reaction of Perfluoro-5,6,7,8-tetrahydroquinoline with Hexafluoropropene in the Presence of Fluoride Ion

All the apparatus was rinsed with acetone and thoroughly dried in an

oven before use. Perfluoro-5,6,7,8-tetrahydroquinoline (1·5g., 4·5 mmole), dry caesium fluoride (5g., 33 mmole) and dry sulpholane (30 ml.) were placed in a flask fitted with a magnetic stirrer, gas-tap, condenser and variable volume reservoir. The flask was evacuated, and then filled with hexafluoropropene gas (16g., 107 mmole), and the mixture was stirred at room temperature until all the gas had been used up, which took about 3 h. Volatiles were then transferred out under vacuum into a cold trap and comprised two materials, one of which was a liquid at room temperature, and the other of which was a white solid. The liquid was oligomers of hexafluoropropene, while the solid was perfluoro-5,6,7,8-tetrahydro-2,4-bisisopropylquinoline. (Yield = 0·5g., 17%). M.p. 48-49°C., b.p. 171°C. (Found: F, 69·3%. $C_{15}NF_{23}$ requires F, 69·24%. Carbon and nitrogen analyses were inconsistent, probably because of loss of olefin from a side chain and incomplete oxidation). Molecular weight = 631. Infra-red spectrum No. 28. N.M.R. spectrum No. 20. Vapour phase chromatography at 200°C showed only one component.

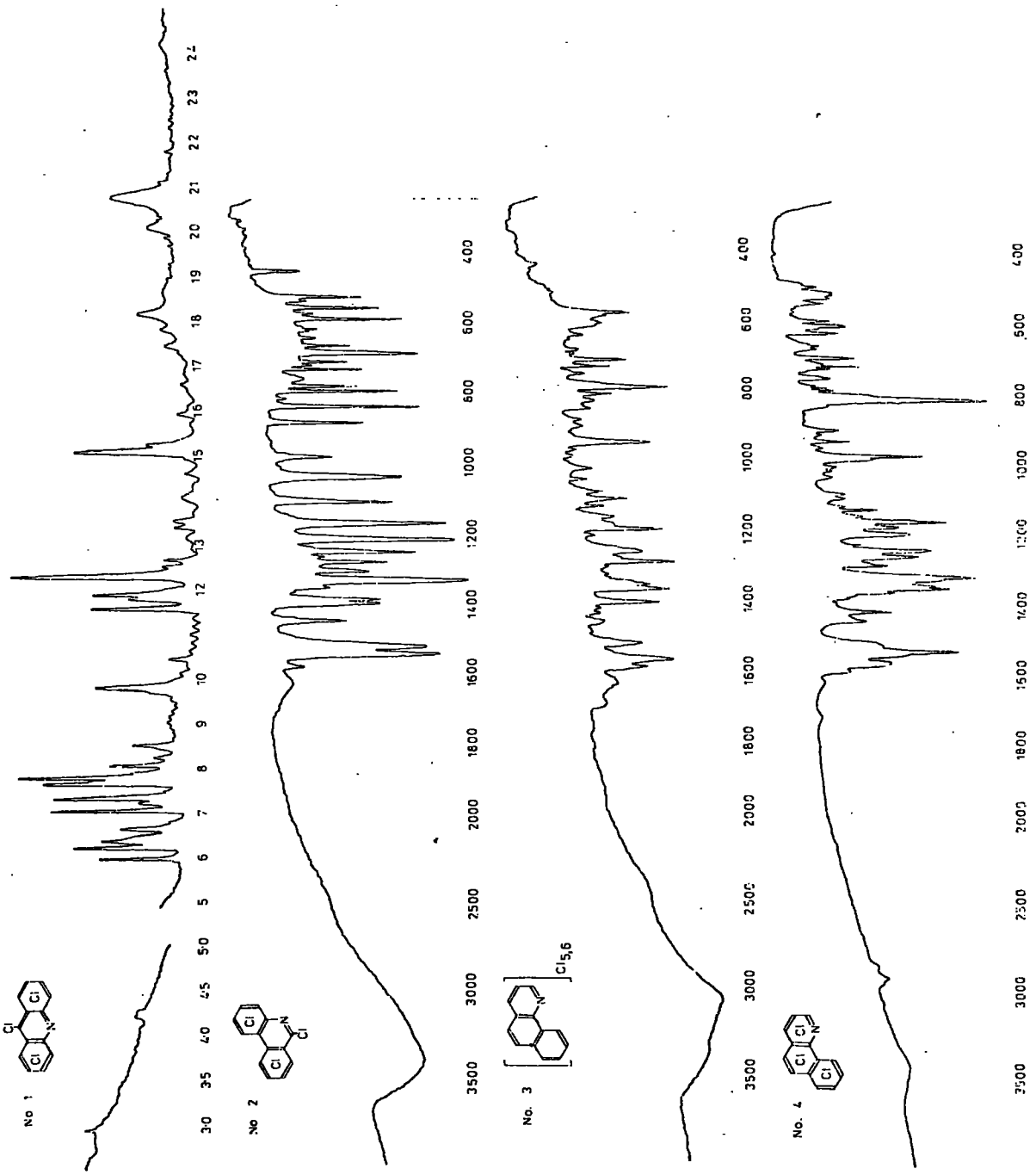
APPENDICES

APPENDIX 1

Infra-red Spectra

Spectrum No.	Compound	State
1	Nonachloroacridine	KBr Disc
2	Nonachlorophenanthridine	KBr Disc
3	Partially chlorinated 7,8-benzoquinolines	KBr Disc
4	Nonachloro-7,8-benzoquinoline	KBr Disc
5	Octachloro-9-acridanone	KBr Disc
6	Octachloro-6-phenanthridanone	KBr Disc
7	Octachloro-9-methoxyacridine	KBr Disc
8	Octachloro-9-ethyliminoacridan	KBr Disc
9	Octachloro-6-methoxyphenanthridine	KBr Disc
10	Octachloro-6-diethylaminophenanthridine	KBr Disc
11	1,2,3,4,5,6,7,8-Octachloroacridine	KBr Disc
12	9-n-Butyl-1,2,3,4,5,6,7,8-octachloroacridan	KBr Disc
13	Nonachlorobiphenyl-2-cyanide	KBr Disc
14	Hexachloro-2-methoxyquinoline	KBr Disc
15	Pentachloro-2,4-dimethoxyquinoline	KBr Disc
16	Hexachloro-2-diethylaminoquinoline	Contact Film
17	Hexachloro-1-methoxyisoquinoline	KBr Disc
18	Hexachloro-1-diethylaminoisoquinoline	KBr Disc
19	2,3,6,7,8-Pentachloroquino-[4,5-cd]-1,2-dithiole	KBr Disc
20	Aminohexachloronaphthalene	KBr Disc
21	5,6,7,8-Tetrachloroheptafluoroisoquinoline	Contact Film
22	Perfluoro-5,6,7,8-tetrahydroisoquinoline	Contact Film
23	3-Methoxyperfluoro-5,6,7,8-tetrahydroisoquinoline	Contact Film

Spectrum No.	Compound	State
24	1,3-Dimethoxyperfluoro-5,6,7,8-tetrahydro-isoquinoline	Contact Film
25	3-Diethylaminoperfluoro-5,6,7,8-tetrahydro-isoquinoline	Contact Film
26	Perfluoro-5,6,7,8-tetrahydro-1,3-bisisopropylisoquinoline	Contact Film
27	3-Bromoperfluoro-5,6,7,8-tetrahydroiso-quinoline	Contact Film
28	Perfluoro-5,6,7,8-tetrahydro-2,4-bisisopropylquinoline	Contact Film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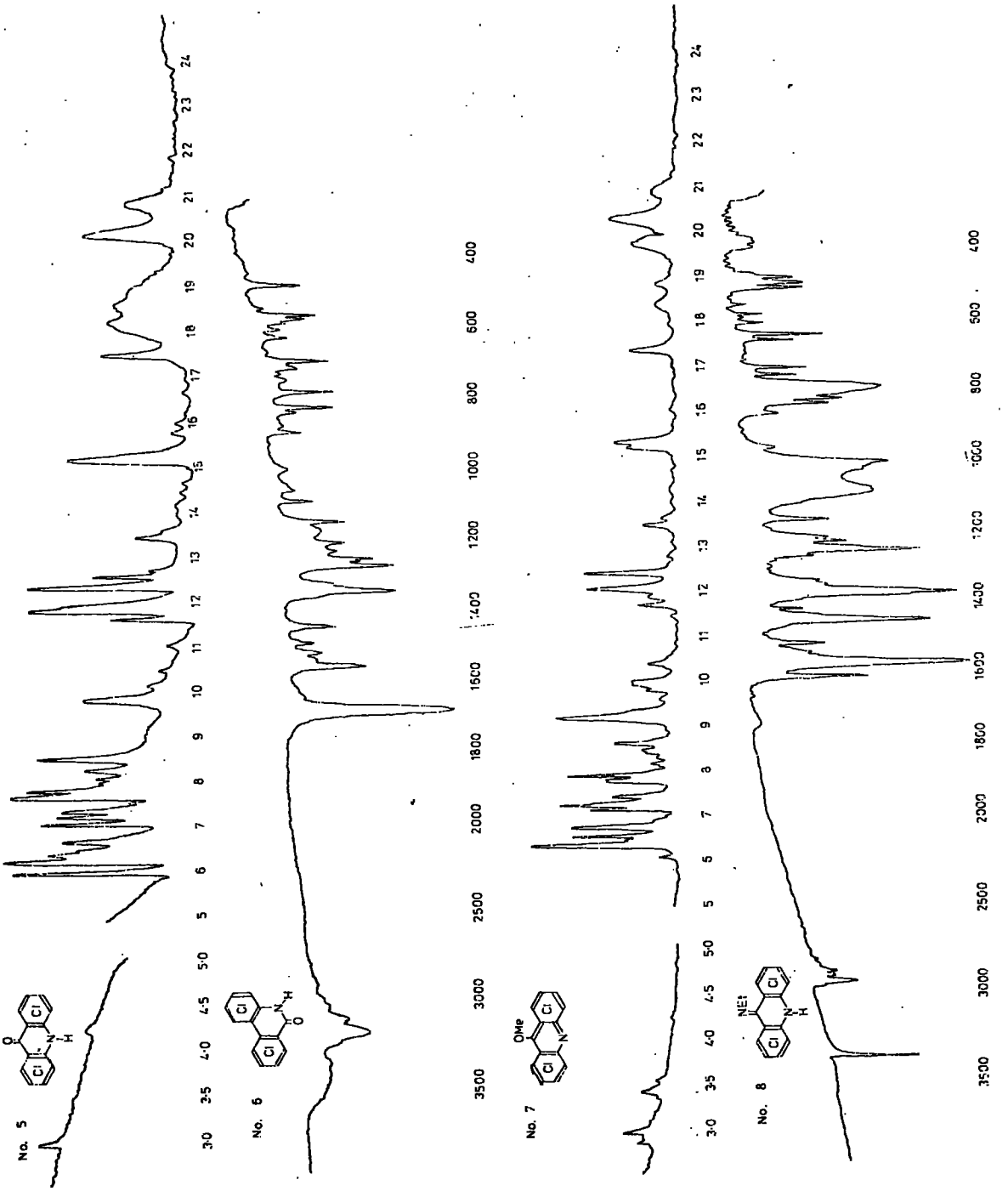
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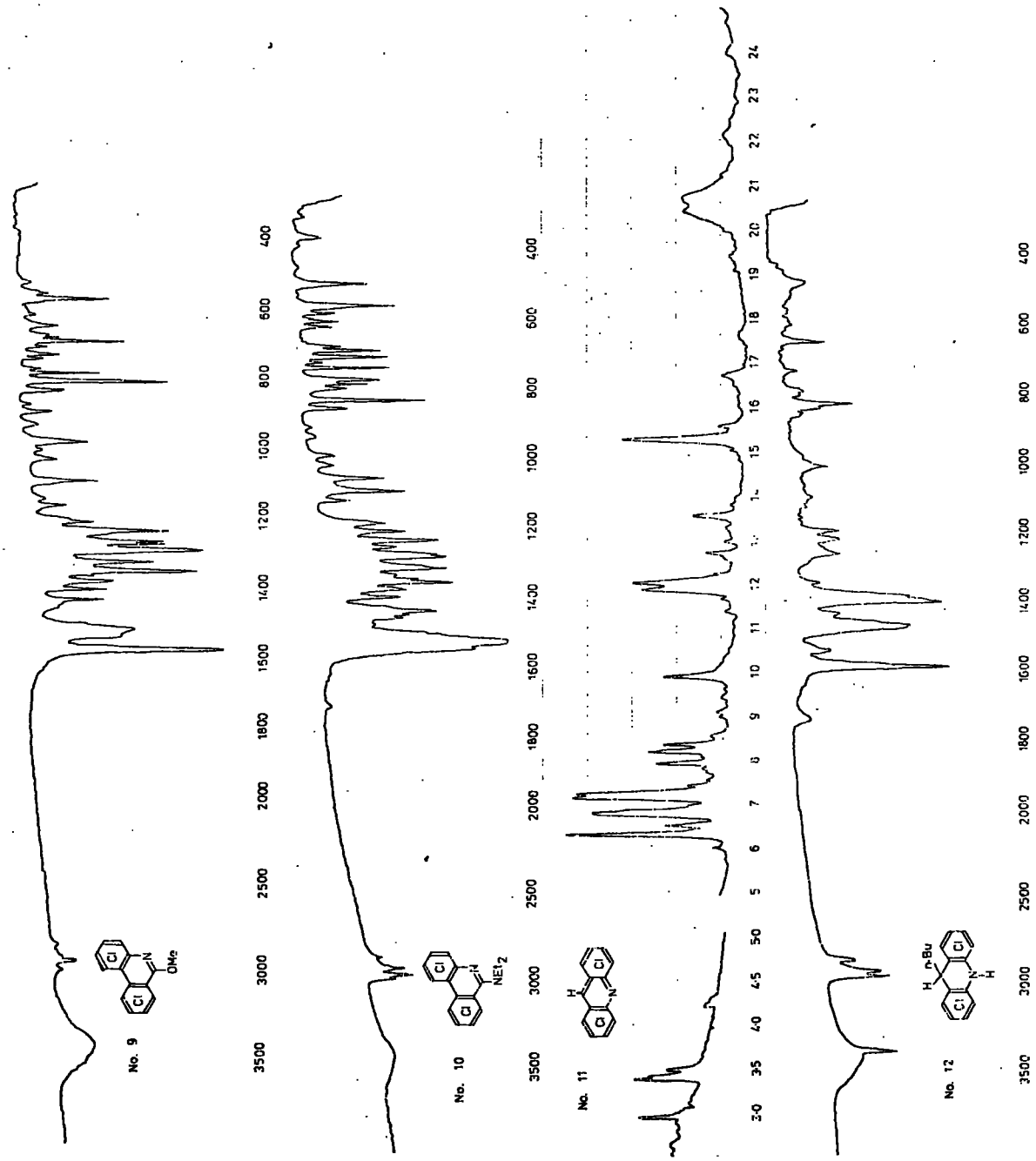
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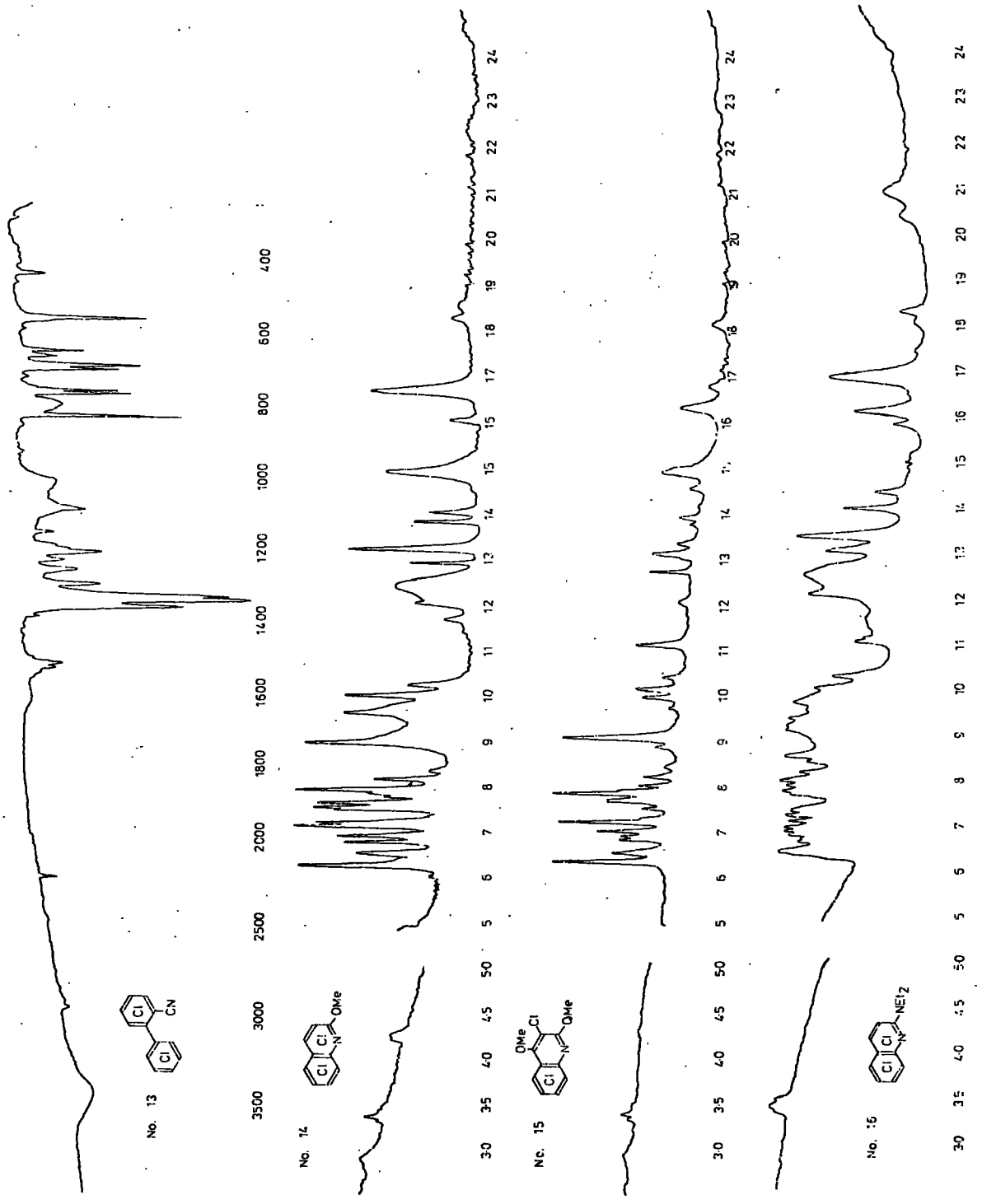
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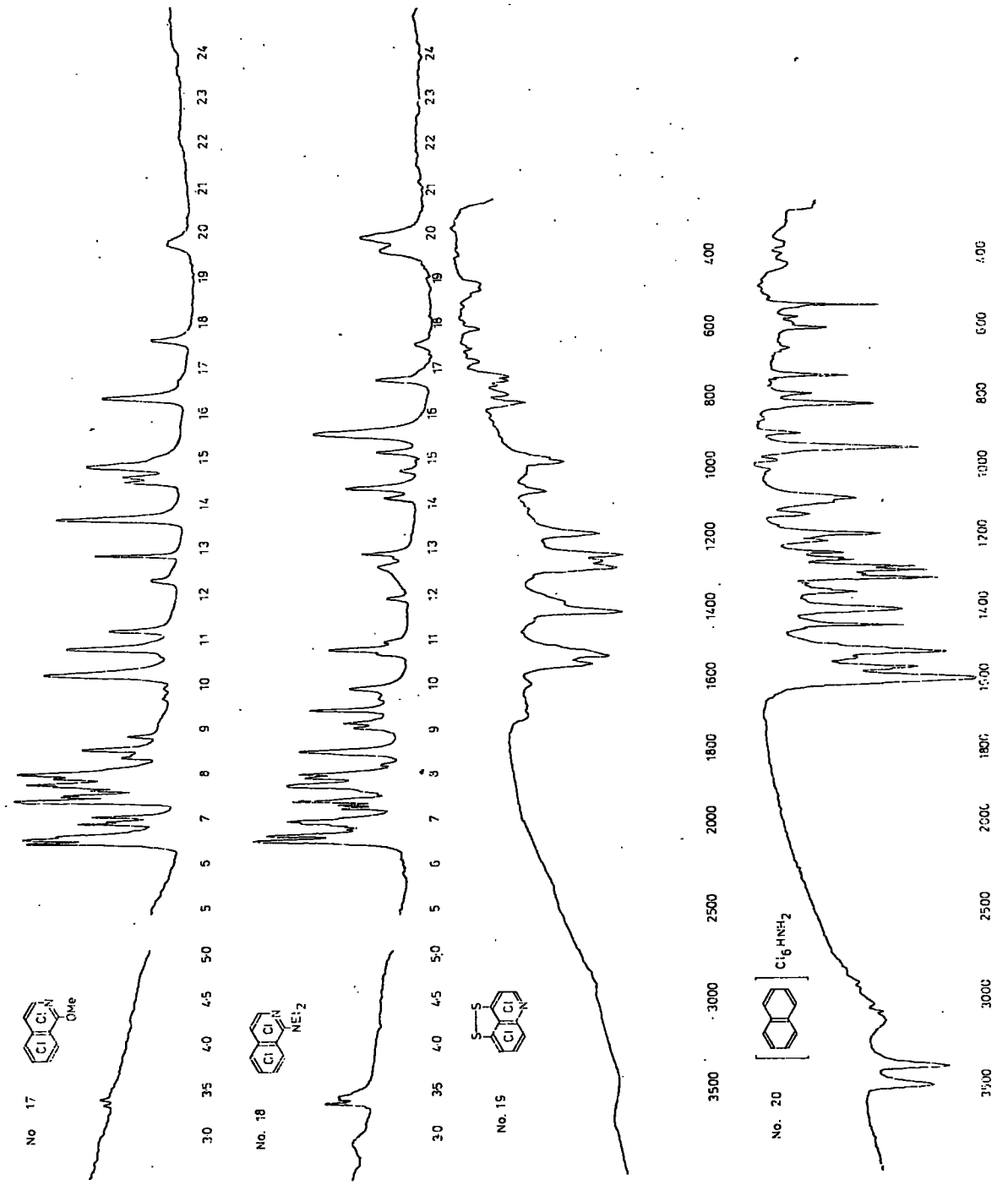
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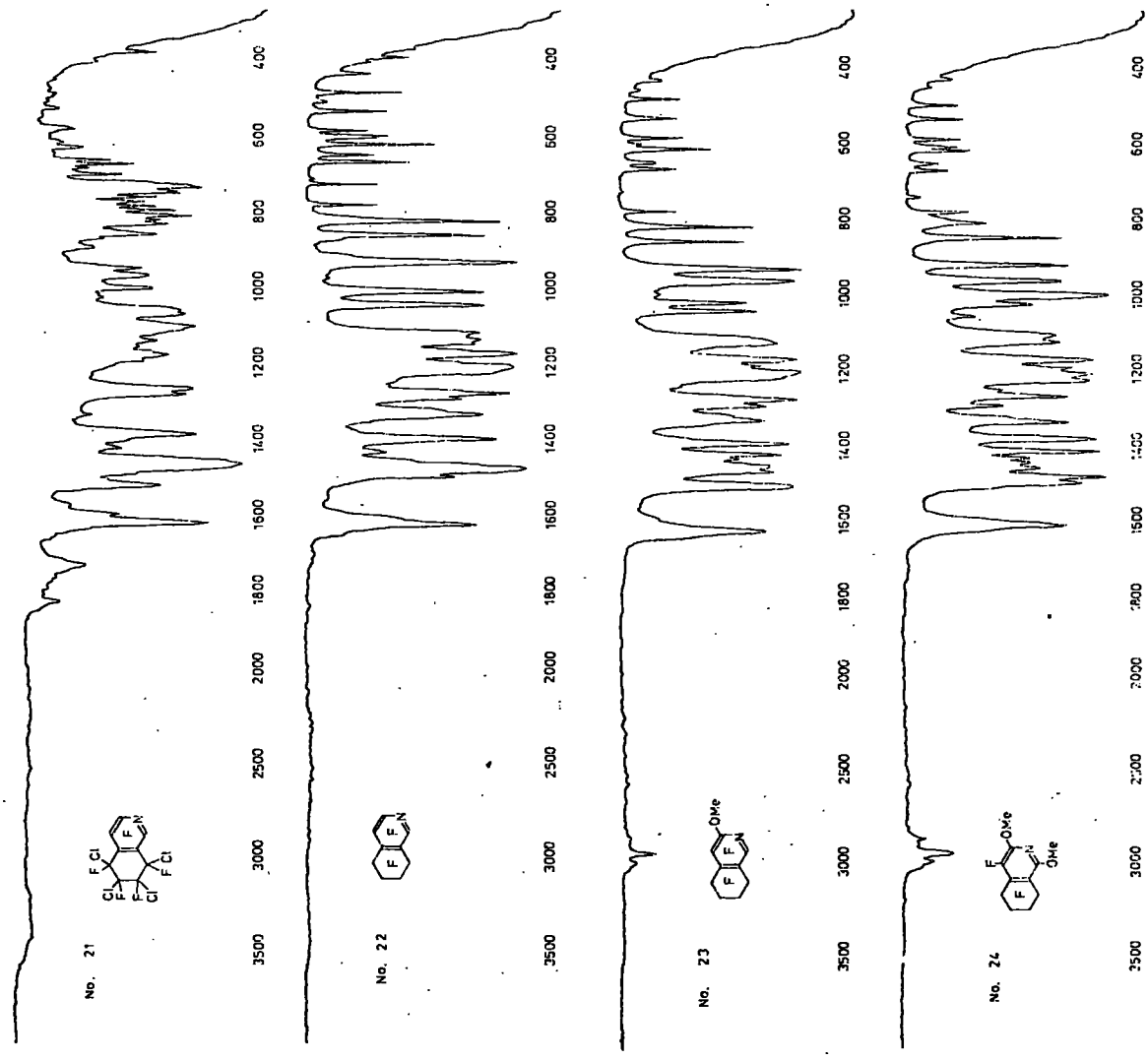
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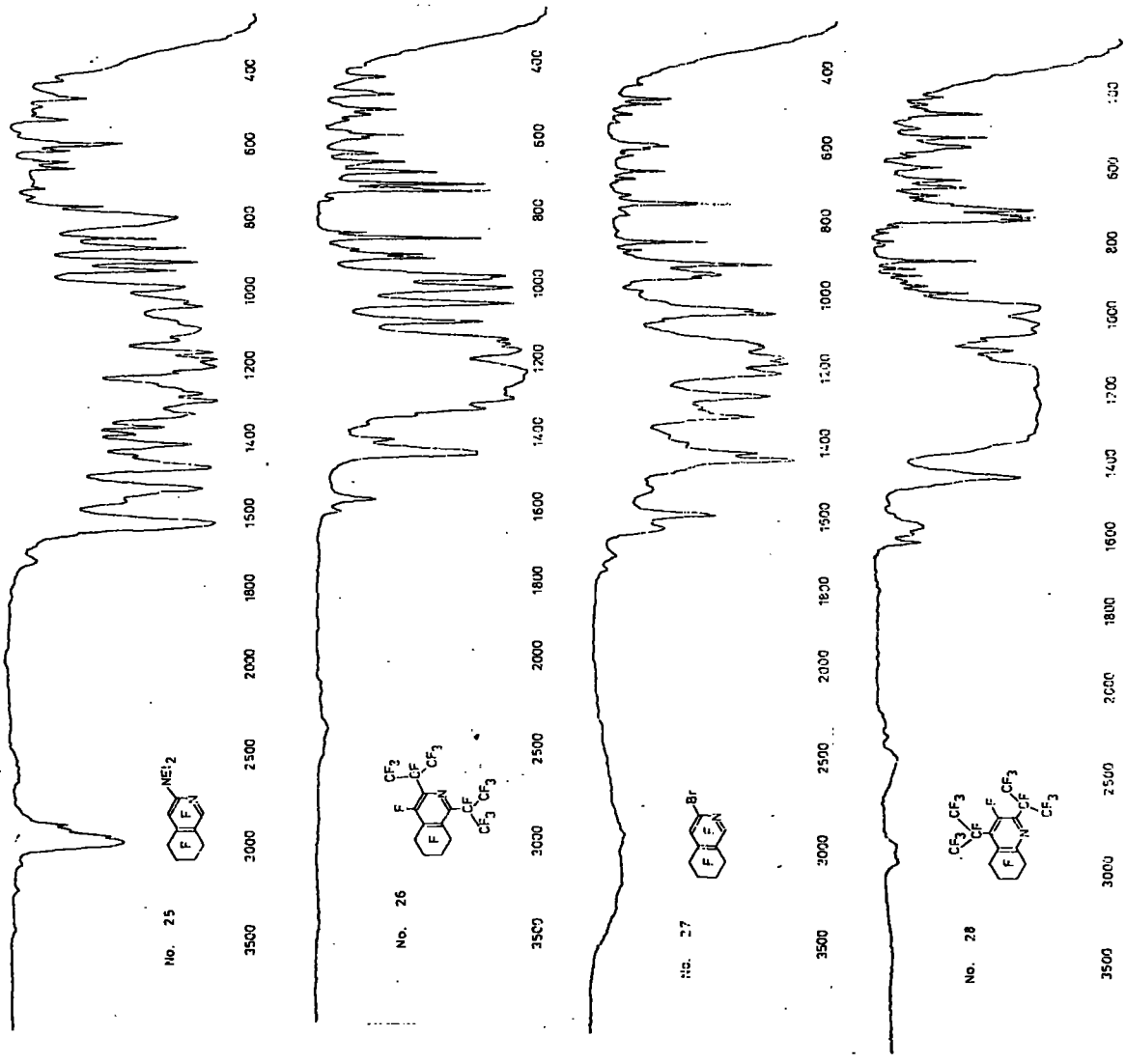
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1000
800
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400

APPENDIX 2

A Note on Mass Spectra

Many of the compounds described in this thesis contain chlorine, for which more than one isotope is stable and reasonably naturally abundant. The parent peaks of these compounds show a group of peaks according to whether ^{35}Cl or ^{37}Cl isotopes are present in the molecular ion. If there is only one chlorine atom in the molecule, then the molecular ion will appear as:

because there are roughly three times as many ^{35}Cl atoms as ^{37}Cl atoms in natural abundance samples. With more than one chlorine atom, the molecular ion will appear as a more complex pattern of peaks, separated by two mass units.

The molecular weights quoted in this thesis are based on the molecule, in which all of the chlorine atoms are of the ^{35}Cl isotope, and are therefore the lowest mass peak in the mass spectrum of the molecular ion. The intensity pattern of the peaks in the molecular ion is highly characteristic of the number of chlorine atoms present in the molecule, and the number of chlorine atoms present in the molecules have been quoted from this means of measurement, using published tables of intensity patterns for chlorine and bromine containing compounds.[223]

Bromine is like chlorine in having two stable isotopes, separated by two mass units, ^{79}Br and ^{81}Br, but they are of approximately equal abundance, so that if one bromine atom is present in the molecule, then the molecular ion appears as:

As with chlorine compounds, the molecular weights of bromine containing compounds, quoted in this thesis, are based on the lower mass isotope, ^{79}Br, and the mass spectrum has been used to identify the number of bromine atoms present in the molecules.

Most of the halogenated compounds described in this thesis have quite stable molecular ions, so that the parent peak in the mass spectrum is normally strong and clearly seen. This is particularly true of highly chlorinated compounds. The amount of fragmentation is normally small, and occurs by successive loss of halogen atoms.

Exceptions to this are compounds with a fairly large and easily lost side chain, such as an n-butyl group. With these compounds the parent peak may not be seen, and an important fragmentation route is by breakdown of the side chain, such as by loss of an alkene.

APPENDIX 3

N.M.R. Spectra

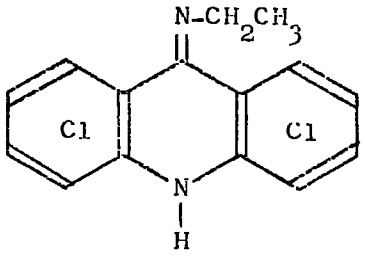
Spectrum No.	Compound	Nucleus	Solvent
1	Octachloro-9-ethyliminoacridan	^{1}H	Chlorobenzene
2	Octachloro-6-diethylamino-phenanthridine	^{1}H	Carbon Tetrachloride
3	9-n-Butyl-1,2,3,4,5,6,7,8-octachloroacridan	^{1}H	Carbon Tetrachloride
4	Hexachloro-2-methoxyquinoline	^{1}H	Carbon Tetrachloride
5	Pentachloro-2,4-dimethoxy-quinoline	^{1}H	Carbon Tetrachloride
6	Hexachloro-2-diethylamino-quinoline	^{1}H	Carbon Tetrachloride
7	Hexachloro-2-diethylamino-quinoline	^{13}C	Deuterochloroform
8	Hexachloro-1-methoxyiso-quinoline	^{1}H	Carbon Tetrachloride
9	Hexachloro-1-methoxyiso-quinoline	^{13}C	Deuterochloroform
10	Hexachloro-1-diethylaminoiso-quinoline	^{1}H	Carbon Tetrachloride
11	5,6,7,8-Tetrachloroheptafluoro-isoquinoline	^{19}F	Liquid
12	3-Methoxyperfluoro-5,6,7,8-tetrahydroisoquinoline	^{1}H	Acetone
13	3-Methoxyperfluoro-5,6,7,8-tetrahydroisoquinoline	^{19}F	Acetone
14	1,3-Dimethoxyperfluoro-5,6,7,8-tetrahydroisoquinoline	^{1}H	Carbon Tetrachloride
15	1,3-Dimethoxyperfluoro-5,6,7,8-tetrahydroisoquinoline	^{19}F	Acetone

Spectrum No.	Compound	Nucleus	Solvent
16	3-Diethylaminoperfluoro-5,6,7,8-tetrahydroisoquinoline	^{1}H	Liquid
17	3-Diethylaminoperfluoro-5,6,7,8-tetrahydroisoquinoline	^{19}F	Liquid
18	Perfluoro-5,6,7,8-tetrahydro-1,3-bisisopropylisoquinoline	^{19}F	Liquid
19	3-Bromoperfluoro-5,6,7,8-tetrahydroisoquinoline	^{19}F	Acetone
20	Perfluoro-5,6,7,8-tetrahydro-2,4-bisisopropylquinoline	^{19}F	Acetone

All shifts are given in p.p.m. and coupling constants in Hz.

Tentative assignments are in brackets.

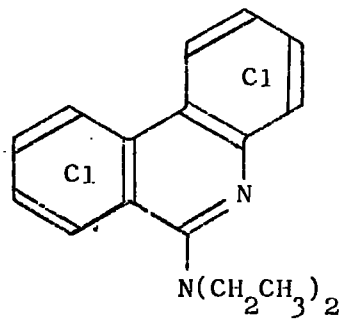
1. Octachloro-9-ethyliminoacridan



^1H	Shift	Assignment
	0·9	CH_3
	6·3	CH_2

$$J_{CH_2-CH_3} = 7$$

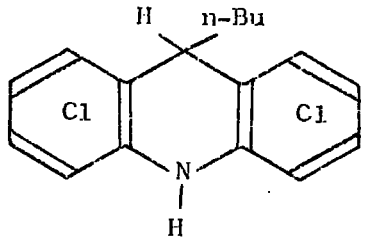
2. Octachloro-6-diethylaminophenanthridine



^1H	Shift	Assignment
	1·3	CH_3
	3·6	CH_2

$$J_{CH_2-CH_3} = 8$$

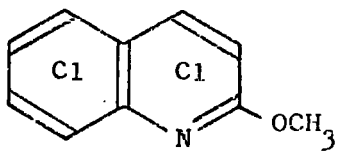
3. 9-n-Butyl-1,2,3,4,5,6,7,8-octachloroacridan



^1H	Shift	Assignment
	0·9	CH_3
	1·1-1·7	$(CH_2)_3$
	4·9	9
	7·5	N-H

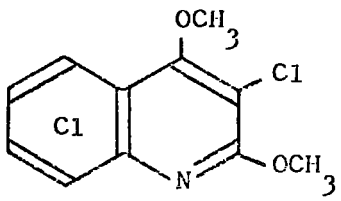
$J_{CH_2-CH_3} = 3$; $J_{9H-CH_2} = 7$; $J_{9H-NH} = 7$

4. Hexachloro-2-methoxyquinoline



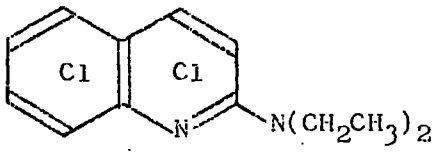
^1H	Shift	Assignment
	4·3	OCH_3

5. Pentachloro-2,4-dimethoxyquinoline



^1H	Shift	Assignment
	5·2	$(2\text{-}OCH_3)$
	5·4	$(4\text{-}OCH_3)$

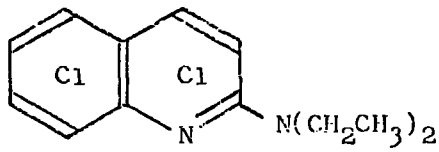
6. Hexachloro-2-diethylaminoquinoline



^{1}H	Shift	Assignment
	1·3	CH_3
	3·8	CH_2

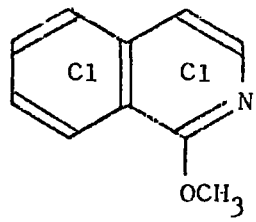
$J_{CH_2-CH_3} = 7$

7. Hexachloro-2-diethylaminoquinoline



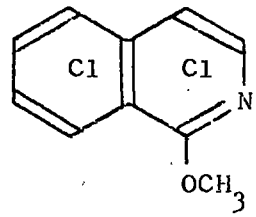
^{13}C	Shift	Assignment
	13·0	CH_3
	44·8	CH_2
	119·5	3 or 10
	121·9	10 or 3
	127·3	5,6,7 or 8
	128·9	5,6,7 or 8
	130·3	5,6,7 or 8
	133·5	5,6,7 or 8
	139·6	4 or 9
	141·3	9 or 4
	155·1	2

8. Hexachloro-1-methoxyisoquinoline



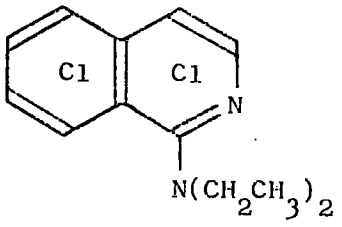
^{1}H	Shift	Assignment
	4·3	OCH_3

9. Hexachloro-1-methoxyisoquinoline



^{13}C	Shift	Assignment
	54·7	OCH_3
	113·0	4 or 9
	114·7	9 or 4
	125·2	5 or 8
	127·3	8 or 5
	130·4	6 or 7
	131·2	7 or 6
	135·6	10
	142·5	3
	153·4	1

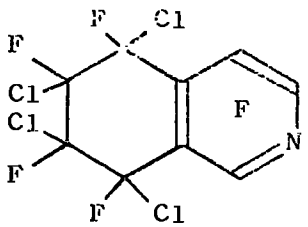
10. Hexachloro-1-diethylaminoisoquinoline



^1H	Shift	Assignment
	1·3	CH_3
	3·7	CH_2

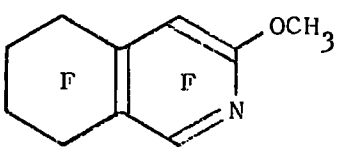
$J_{CH_2-CH_3} = 7$

11. 5,6,7,8-Tetrachloroheptafluoroisoquinoline



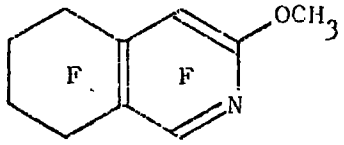
^{19}F	Shift	Assignment
	60·7	1
	79·7	3
	94·0	a CFCl
	106·2	two CFCl's
	142·4	4 + a CFCl

12. 3-Methoxyperfluoro-5,6,7,8-tetrahydroisoquinoline



^1H	Shift	Assignment
	3·8	OCH_3

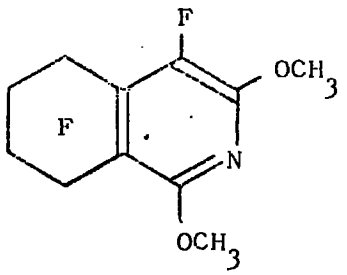
13. 3-Methoxyperfluoro-5,6,7,8-tetrahydroisoquinoline



^{19}F	Shift	Assignment
	69·3	1
	107·6	CF_2 8
	110·8	CF_2 5
	137·3	CF_2 6 + 7
	144·6	4

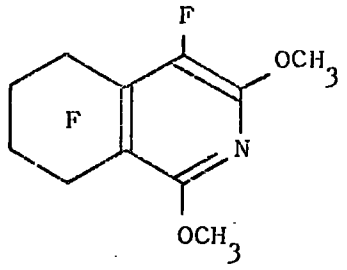
$J_{1-4} = 29$; $J_{4-5} = 18$; $J_{1-8} = 18$

14. 1,3-Dimethoxyperfluoro-5,6,7,8-tetrahydroisoquincline



^{1}H	Shift	Assigment
	3·8 (broad)	two OCH_3

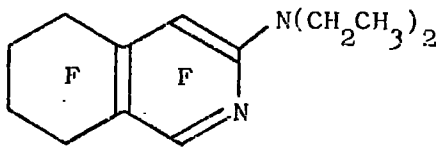
15. 1,3-Dimethoxyperfluoro-5,6,7,8-tetrahydroisoquinoline



^{19}F	Shift	Assignment
	109·2	CF_2 8
	110·4	CF_2 5
	136·8	CF_2 6 + 7
	153·9	4

$J_{4-5} = 19$

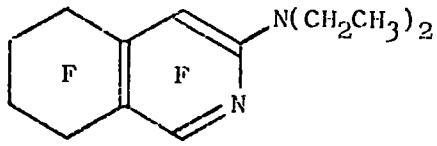
16. 3-Diethylaminoperfluoro-5,6,7,8-tetrahydroisoquinoline



^{1}H	Shift	Assignment
	1·2	CH_3
	3·5	CH_2

$J_{CH_2-CH_3} = 7$

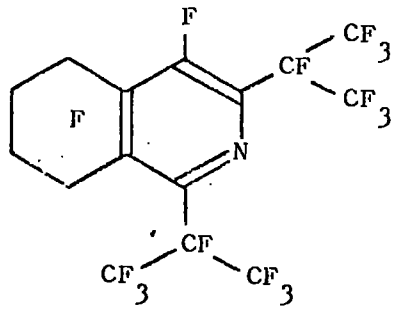
17. 3-Diethylaminoperfluoro-5,6,7,8-tetrahydroisoquinoline



^{19}F	Shift	Assignment
	66·2	1
	105·5	CF_2 8
	110·9	CF_2 5
	136	CF_2 6 + 7
	143·2	4

J_{1-4} = 28; J_{4-5} = 27; J_{1-8} = 18

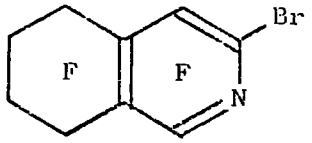
18. Perfluoro-5,6,7,8-tetrahydro-1,3-bisisopropylisoquinoline



^{19}F	Shift	Assignment
	75·6	CF_3 x 2
	76·4	CF_3 x 2
	103·3	CF_2 8
	107·8	CF_2 5
	113·9	4
	137·0	CF_2 6 + 7
	182·8	tertiary F 1
	187·0	tertiary F 3

J_{4-5} = 20; $J_{4\text{-tertiary F 3}}$ = 55; $J_{8\text{-tertiary F 1}}$ = 76

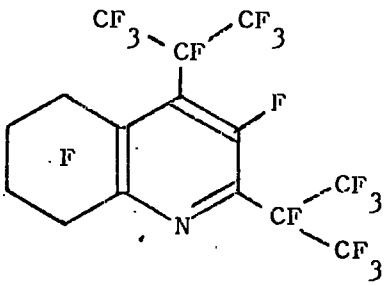
19. 3-Bromoperfluoro-5,6,7,8-tetrahydroisoquinoline



^{19}F	Shift	Assignment
	67·3	1
	109·6	CF_2 8
	110·8	CF_2 5
	117·4	4
	137·0	CF_2 6 + 7

$J_{1-4} = 30$; $J_{4-5} = 16$; $J_{1-8} = 16$

20. Perfluoro-5,6,7,8-tetrahydro-2,4-bisisopropylquinoline



^{19}F	Shift	Assignment
	~75	CF_3 x 4
	102·7	CF_2 5
	109·1	CF_2 8
	109·8	3
	~136	CF_2 6 + 7
	~175	tertiary F 2 + 4

$J_{5\text{-tertiary F } 4} = 80$

APPENDIX 4

Ultra-violet Spectra

Spectrum No.	Compound
1	6-Phenanthridanone
2	Nonachloroacridine
3	Nonachlorophenanthridine
4	Nonachloro-7,8-benzoquinoline
5	Octachloro-9-acridanone
6	Octachloro-6-phenanthridanone

All spectra were recorded in solution in spectrosol carbon tetrachloride, and at the ambient temperature of the spectrometer. All peaks in the range 250 to 700 nm are given, and peaks which are shoulders are marked (s).

1. 6-Phenanthridanone

Wavelength nm	Molar Absorbance
337	1400
322	1700
311	1300
273 (s)	2000
261	3000

2. Nonachloroacridine

Wavelength nm	Molar Absorbance
442	3000
421	4000
397	5500
377	3200
359 (s)	2000
325 (s)	1500
295	118,000
285 (s)	48,600
273 (s)	17,400

3. Nonachlorophenanthridine

Wavelength nm	Molar Absorbance
403 (s)	16,800
386 (s)	38,800
354	84,100
320 (s)	263,300
288	343,800

4. Nonachloro-7,8-benzoquinoline

Wavelength nm	Molar Absorbance
395 (s)	1000
322 (s)	10,500
302 (s)	14,700
285	15,800
286 (s)	16,300
261	20,500

5. Octachloro-9-acridanone

Wavelength nm	Molar Absorbance
444 (s)	900
422 (s)	1200
399	3300
382 (s)	2400
324	2000
294	34,100
274	29,600

6. Octachloro-6-phenanthridanone

Wavelength nm	Molar Absorbance
370	1500
294 (s)	4000
266	8100

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